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Editorial

Ageing and radiation

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The starting point of my own reflections on the general problem of ageing is the commonly held view that whole-body irradiation of an animal can, in certain circumstances, speed up natural ageing. This generalization has only been checked experimentally to a limited degree. Certainly, irradiated animals normally have a reduced survival time; and after a single dose of irradiation or after lifetime low-level chronic irradiation the pathology at death is broadly the same as in unirradiated control animals. But even using only terminal data of this sort for CBA mice, it is possible to argue that there is an intrinsic process of ageing, enhanced by radiation, which operates from the start of life and is virtually complete by the time the changes of old age begin to appear; until then the process has little outward physiologic manifestation or effect on survival fitness. The argument is quite simple, but first it is necessary to clear a little ground and establish a common conceptual currency.

Two basic questions may be posed: Why does an animal die? Why is there a variation in the age at death of comparable individual animals? One type of answer emphasizes the element of randomness in mortality, and the individuals in a population are often tacitly assumed to be identical. The age-specific death rate, the so-called "force of mortality," is often interpreted as the probability that *any* survivor will die in a unit interval of time at that age. The observed progressive increase of the force of mortality, after a certain age, is attributed to a progressive decline in the physiologic state or vitality of the population and the individuals thereof. The logarithm of the mortality rate, the Gompertz function, increases approximately linearly with age, and so it has been an attractive idea to regard this quantity as an intrinsic index of physiologic age.

A quite different type of answer to the two basic questions concentrates attention on the individual; his life span in any given environment is predetermined by his initial genetic endowment. Merely to recognize the existence of this theoretical possibility is of considerable importance, because it then has to be admitted that the progressive increase with age in the age-specific death rate may result merely from the form of the distribution of individual life spans in the population. The concept of a "force of mortality" would then be out of place and there need be no relation between the Gompertz function and the physiologic state either of individuals or of the surviving population as a whole. In most quantitative deterministic theories, ageing is regarded as some process of change within cells, probably in their genetic apparatus. It is clear, however, that the fate of the individual cannot be considered solely in terms of the fate of a component cell. Even though changes within cells may be the root cause of ageing, it would be in-

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sufficient to consider only the primary process, without reference to the whole sequence of events in the complex of interacting physiologic systems.

In practice, both random and deterministic factors undoubtedly play some part. For the human white female population of the United States at present the difference in age at death of identical twins is much less than the standard deviation over the whole population. On the other hand, there has been a significant reduction in mortality during the past hundred or so years in most economically developed countries. The reduction is chiefly in the acute causes of death and has been most marked in early and middle life; the chronic degenerative causes have shown a much smaller change. Hardin B. Jones has argued from such facts that there is a causal relation between disease experience and subsequent susceptibility to disease, but, so far, animal experiments have provided no definite confirmation of this theory.

My own view is that even if all adverse external influences could be removed, an intrinsic process of ageing would remain, which is fundamental, inevitable, and irreversible. The process proceeds in two successive stages, induction and development, which together occupy the whole lifetime. During induction, changes occur within individual cells; these naturally occurring changes can also be produced by radiation. Because of homeostatic regulation, the production of the changed cells, which may or may not be viable, produces little physiologic impairment until a certain level of inductive change has been reached. Then homeostasis breaks down rather rapidly and the second stage, development, sets in. It involves a different level of organization and consists in physiologic interactions which proceed autonomously and autocatalytically, entailing rapid physiologic impairment culminating in death; development thus corresponds to senescence. Once it has been triggered, further inductive change is superfluous, so that further irradiation at this stage is ineffective, provided that it is not sufficiently intense to have direct physiologic effects. The primary process of induction is genetically determinate and little influenced by random factors; the second process of development may, because of its greater complexity, be subject to such factors.

One of the essential features which distinguishes this picture of ageing is the approximate constancy of physiologic competence for survival during induction, which in mice occupies about 80 per cent of the lifetime; physiologic ageing is mainly a phenomenon of senescence. The opposite assumption which has usually been made that all of the injury produced by the simple passage of time or by whole-body irradiation is necessarily expressed as proportional physiologic injury has, in my opinion, hindered the understanding of the problem, especially the analysis into reparable and irreparable injury. As Shock has pointed out, some indices of physiologic capacity are more or less constant throughout life; others appear to show a decline, but such data are usually obtained from different groups of individuals at different ages: "What we do not know, of course, is what happens to a single individual as he progresses through his life cycle." The range of variation between individuals of the same age is almost large enough to admit the possibility that there is little change in the individual before senescence. In any case, some of these indices refer to maximum physiologic capacity, which may have relevance only to survival from the more extreme "accidents" in the presenescent period. The important question is whether there is a marked increase in the rate of loss of physiologic capacity during senescence.

The experimental data which suggested to me the foregoing scheme were obtained in survival studies of chronically irradiated CBA mice under carefully kept conditions so that external disturbing factors were minimized. It is generally found that the mean life shortening of a group of mice or rats is roughly proportional to the mean accumulated radiation dose. It is reasonable to expect, therefore, that the life shortening for one individual will be roughly proportional to his individual accumulated dose. If exposed to a given dose rate throughout life, the naturally longer lived animals would receive a larger accumulated dose, and their absolute life shortening would exceed the average, but the proportional life shortening would be

the same for all. The cumulative mortality curve against time for an irradiated group would thus correspond to that of a control group, but with the time axis contracted. The standard deviation of survival time would be decreased by radiation in the same proportion as the mean survival time itself. Conversely, the slope of the Gompertz plot would be increased. In fact, however, these features were not found with CBA mice. Up to about 15 rems per day, there was no reduction in dispersion of survival times even though the mean survival time was nearly halved; the cumulative mortality curves were merely displaced from each other, not contracted; the Gompertz plots were roughly of equal slope. These results would be explicable if the induction time and radiosensitivity were nearly the same for every member of a group of these genetically homogeneous mice. The effective accumulated dose during induction and the shortening of induction time relative to controls would then be the same for all. The duration of development was unaffected by radiation and was statistically the same for irradiated and control animals; a value of about 180 days was deduced. The Gompertz plots were very steep and roughly linear during the period of development; before that, in the induction period, the slope was much less. Further analytical details may be found in the original paper.

An understanding of the basic process of cellular change during induction would not only be of great theoretical interest but also of practical importance in providing, perhaps, a basis for extrapolation of life-shortening data on animals to man. So far, however, little sure evidence is available from the radiobiologic data. The dose response is linear, which is clearly consistent with a cumulative injury due to irreversible changes in cells. The linearity argues against the primary process being one of chromosome structural damage and would suggest rather somatic gene mutation. The fact that short single doses of X or gamma radiation are some three times as efficient as the same doses delivered chronically at low rates indicates a dose rate factor which is not expected for gene mutation. Moreover, the large size of the "doubling dose" (some thousands of rems) is surprising for a gene mutation unless cell selection for the radiation mutants is much more severe than for the natural mutants. Perhaps the site of the change is not in the chromosomes at all; in some organisms, ageing seems to be a cytoplasmic phenomenon.

It is not known whether the cell change responsible for ageing causes the death of irreplaceable cells, or reduces the competence of cells for certain functions, or whether it results in autoimmune reactions between changed and normal cells or between changed cells themselves. It is also not known whether all the cells of the body are subject to the particular form of change or whether only special systems of cells are important—these latter might constitute the homeostatic systems supposed necessary to keep spontaneous autoimmunity suppressed. The question obviously arises as to whether the primary process is the same in different organisms, even as closely similar, say, as mice and men. If this assumption is made for the latter particular pair, we may note that, according to the simplest theory, the life shortening per rem is numerically equal to the ratio of the rate of cell change produced by unit dose rate to the spontaneous rate. There is no obvious reason why this ratio should be very different for a mouse and a man, and so the life shortening per rem in man may be only 0.08 days, the figure found for mice. It has frequently been assumed that the life shortening per rem in man would be greater than in a mouse in the ratio of the natural life spans, but the logic of this is not apparent. It is also interesting to speculate how the development period of 6 months in the mouse would be extrapolated to man. I leave it to physicians to decide whether a figure of 6 months or some 25 times this, i.e., about 12 years, is a better estimate of the period of senescence in man.

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Clinical communications

A clinical study of shock occurring during acute myocardial infarction An analysis of 58 cases

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Severe shock has been estimated variously to occur in from 7 to 20 per cent of the patients suffering from acute myocardial infarction.[1-7] Its development is a grave complication and is associated with a high mortality rate. The importance of early recognition of this syndrome has been emphasized, since prompt therapy appears to increase the chance for survival. The time at which shock occurs after the development of an acute myocardial infarction and the natural life history of this condition is therefore of great importance in its recognition and management.

It is the purpose of the present paper to report a clinical study of 58 cases of this syndrome. Adequate data were available to permit a detailed study of cardiogenic shock, of its frequency of occurrence, clinical characteristics, mortality, and various features affecting the prognosis.

Clinical material, methods, and criteria

Seven hundred and fourteen cases of acute myocardial infarction were surveyed in the present study. There were 546 men and 168 women; 161 patients succumbed, a mortality rate of 22.5 per cent. The diagnosis of acute myocardial infarction was made on the basis of a typical clinical history plus characteristic electrocardiographic findings. Additional confirmation was obtained by autopsy in 14 of the 29 patients who succumbed after myocardial infarction.

The age distribution ranged from the fifth through the ninth decade (Table I). The greatest number of cases occurred in the sixth decade. The ages varied from 43 to 83 years. Seventeen patients in the group with shock were hypertensive or were known to have been hypertensive prior to the onset of shock; in many others, preceding hypertension was suspected but not proved.

Frequent determinations of the blood pressure were made during the first week of the hospital stay. In many patients, during the first 48 to 72 hours, these readings were made at intervals of 1 hour, both day and night. The criteria for the diagnosis of shock in patients who were suffering from acute myocardial infarction included the following: (1) Definite clinical signs of shock were present; these included sweating, weakness, pallor or cyanosis, absent or small volume pulse, moderate tachycardia, nausea, and often a dulled sensorium. (2) The level of blood pressure fell to 80 mm. systolic or below; in patients previously hypertensive, readings below 90 mm. systolic were considered as shock levels.

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Table I. *Myocardial infarction with shock. Age distribution and mortality by decades*

Age group (yr.)	*Number of patients*	*Number of deaths**	*Mortality (%)*
30–39	0		
40–49	5 (9%)	1	20
50–59	25 (43%)	9	36
60–69	13 (22%)	8	62
70–79	13 (22%)	11	85
80–89	2 (3%)	0	—

*In all fatal cases, death was attributable directly to the effects of cardiogenic shock.

Hypotension alone was not considered prima facie evidence of shock, since, as will be seen, some patients exhibited hypotension without other confirmatory signs of the shock state. In addition, patients in whom the fall in blood pressure could be attributed to some other primary initiating cause, such as hemorrhage, pulmonary embolism, severe tachycardia, acute cerebrovascular accident, or marked cardiac failure, were not included in the present series. Fifty-eight patients with shock after acute myocardial infarction met these criteria, and are the subject of the present study. Patients who lived for 10 days after therapy for shock was discontinued were classified as survivors.

Results

Mortality. Fifty-eight patients (8 per cent) of the group of 714 with acute myocardial infarction developed shock. The total mortality in this group with shock was 50 per cent. Two of these 58 patients succumbed before treatment was begun, and 2 received inadequate therapy (with l-norepinephrine being administered for less than 1 hour prior to death). In the other 54 patients who received adequate therapy the mortality was found to be 46 per cent (Table II). This mortality is comparable to that found in other adequately treated groups,[8-21] and is slightly more favorable than that reported in some series. It is also a marked improvement over the survival rate to be expected in patients treated by nonspecific means without vasopressor substances, in whom the mortality has been reported to range from 70 to as high as 93 per cent.[2-7]

Time of onset of shock. In the great majority of instances, the time of onset of the myocardial infarction could be established with reasonable certainty. In 62 per cent of the patients, shock followed the onset of myocardial infarction within 24 hours (Fig. 1). Within 72 hours the vast majority of cases of shock had developed; 91 per cent of the cases had appeared by this time.

As has been reported previously,[2] a few cases may be delayed until later in the course of the illness. One case occurred on the fourth, one on the fifth, two on the sixth, and one on the eleventh day after the onset of acute myocardial infarction. If the majority of cases of shock are to be detected promptly, therefore, patients with acute myocardial infarction must be observed most closely in the intial period of 72 hours.

Clinical features and classification

Hypotension without shock. In a review of this series of 714 patients, hypotension without clinical signs of shock was encountered occasionally. This hypotensive phase after acute myocardial infarction has been noted by others.[22,23] If clinical signs of shock did not develop, the outcome did not appear to be affected adversely in the present series. A few of this group of patients with hypotension had blood pressure readings as low as 80 or occasionally slightly lower. However, aside from some chest pain, they remained fairly comfortable and warm, were not cyanotic, did not perspire, their color remained good, and shock did not follow. This hypotensive response was not accompanied by evidences of severe cardiac insufficiency, and in most of these patients the blood pressure returned

Table II. *Results of treatment of shock in acute myocardial infarction*

Total number of patients	58	
Total number of deaths	29	50%
Total number of survivors	29	50%
Total number of deaths with adequate treatment*	25	46%
Pressor effect*	47	87%

*Excluding 4 patients with either no vasopressor therapy or inadequate therapy.

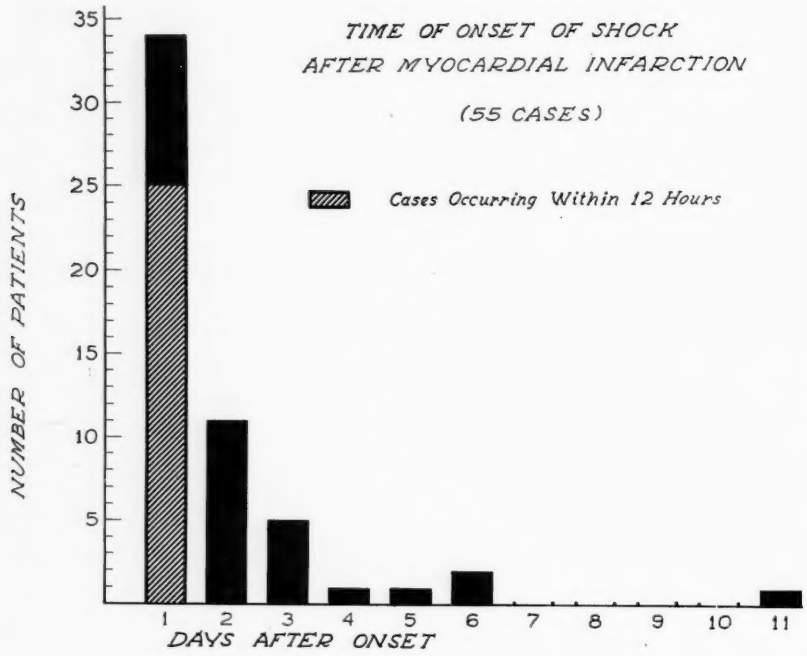

Fig. *1*. Time of onset of shock after development of myocardial infarction.

toward normal during the latter part of their hospital stay. This group of patients was not included in the present study as suffering from shock, and did not appear to have the same prognosis and outlook.

Premonitory shock. Shock which occurred after myocardial infarction did not always arise *de novo*. One of the striking features of the present study was the occurrence of one or more warning episodes of transitory shock, followed by a return of the blood pressure to normal. These premonitory episodes developed one to several hours before deep shock supervened, and were usually only temporary in nature, lasting from several minutes to an hour or two. In many of these instances the blood pressure returned to normal spontaneously, without any specific vasopressor therapy. In a few patients, small amounts of mephentermine sufficed to abolish the brief period of shock. In these patients, typical signs of shock were present, and these clinical signs served to distinguish this group from the previously described group of patients who exhibited only hypotension, without other stigmata of the shock state.

This early transitory state of shock was a striking feature, and preceded the development of deep shock in a significant number (36 per cent) of the patients. The spontaneous return of blood pressure levels to normal, after such brief periods of shock, suggested the operation of a homeostatic mechanism to maintain adequate perfusion pressure in the various organ systems, and to preserve body circulation. The prognostic significance of this early hypodynamic phase of the circulation in acute myocardial infarction, in predicting the subsequent occurrence of persistent shock, is of obvious importance. It frequently appeared to be a warning sign of impending acute circulatory collapse.

Classification of cases. Frank clinical shock with all of its characteristic manifestations was present in all of the patients included in the present series. No patient with mild shock or hypotension alone was included in this group. However, it was possible to separate the patients further into three main groups on the basis of their clinical features and response to therapy. These groups were classified as follows: moderately severe, severe, and fatal. The primary criterion used in differentiating these groups was the response to therapy.

MODERATELY SEVERE SHOCK. The patients with moderately severe shock responded promptly to adequate vasopressor therapy and exhibited a rapid elevation of blood

pressure to normal levels, accompanied by a fairly rapid abolition of the clinical signs of shock. These patients did not require the prolonged use of levarterenol by vein, and usually within a period of 24 hours vasopressor agents could be discontinued, without further deleterious effects. Anuria was uncommon. Oliguria was seen occasionally, but prompt resumption of adequate flow of urine occurred with therapy. An example of the findings and problems encountered in such a patient is given in the following case history.

Case history. A 52-year-old white man who had sustained a previous myocardial infarction 6 years ago developed severe substernal pain, which radiated into the left arm and neck. His blood pressure during the episode of pain, at home, was 200/128 mm. Hg (Fig. 2). On admission to the hospital he was in acute distress and had an ashen color. His blood pressure was 130/80 mm. Hg; the pulse was of good quality. The cardiac rhythm was regular with a rate of 64 per minute; no gallop sounds or murmurs were noted. An electrocardiogram on admission revealed a deep Q wave in Leads II and III, with S-T-segment elevation, confirmed in Lead aV_F. His subsequent tracings revealed the typical evolutionary changes of an acute posterior myocardial infarction.

Three and one-fourth hours after admission he became cold and clammy, and perspired profusely; his pulse became weak, and the blood pressure dropped to 80/50 mm. Hg. An infusion of mephentermine sulfate was started, and within a few minutes his blood pressure returned to normal. His blood pressure then remained within normal limits, and no signs of shock occurred for approximately 8 hours after the infusion was discontinued. He then developed pallor, weakness, and dyspnea, with a blood pressure of 70/56 mm. Hg. A second infusion of mephentermine was begun. When his blood pressure did not rise promptly, an intravenous infusion of levarterenol bitartrate was initiated, and this resulted in a rapid rise of his blood pressure to normal, with disappearance of the signs of shock. The infusion was continued for 14 hours and then terminated, following which his blood pressure remained normal. No evidences of pulmonary edema appeared. His subsequent hospital course was uneventful, and he was discharged in good condition.

COMMENT. This patient exhibited early shock of mild degree, which originally was abolished promptly by the use of mephentermine. He subsequently developed deeper and more persistent shock, which did not respond to mephentermine and necessitated the use of levarterenol. A prompt pressor response with the latter medication occurred, no evidence of congestive failure or arrhythmias appeared, and the output of urine remained adequate.

SEVERE SHOCK. The group of patients with severe shock often required a prolonged period of vasopressor therapy. Many of these patients developed frank clinical congestive heart failure during this period of time, necessitating digitalization. However, with careful therapy, adequate homeostasis was eventually achieved, the vasopressor substances were gradually discontinued, and the patients survived.

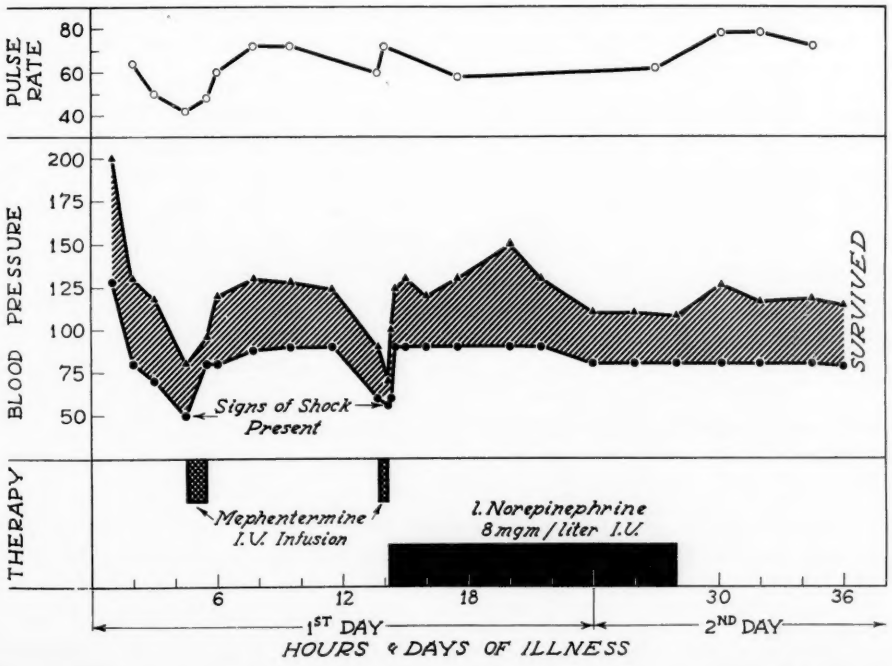

Fig. 2. Fifty-two-year-old man. Moderately severe shock after myocardial infarction (see text).

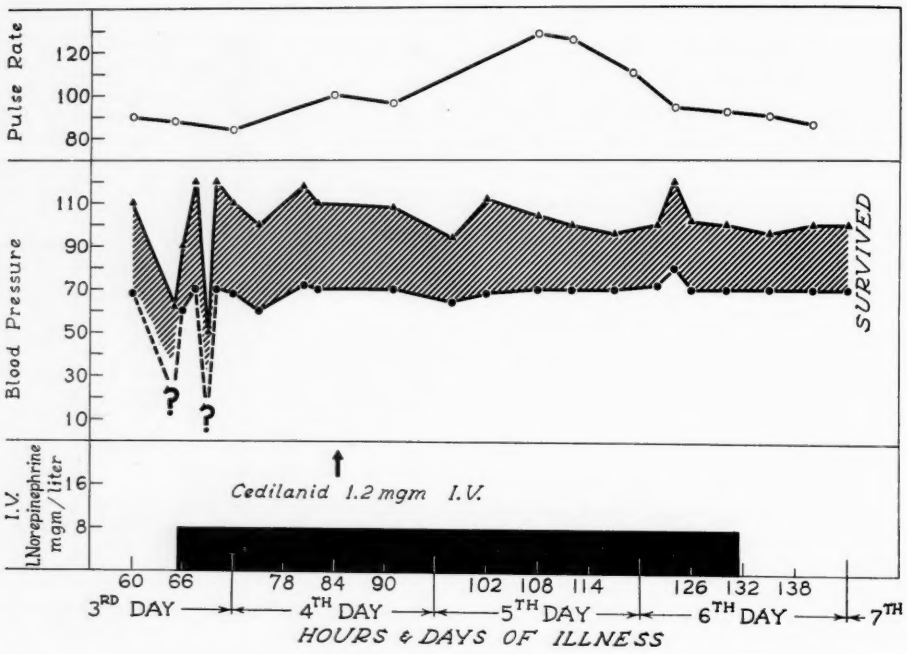

Fig. 3. Sixty-year-old man. Severe shock after myocardial infarction (see text).

Oliguria was frequent, but with adequate therapy, secretion of urine was generally resumed, although sometimes it was diminished for variable periods. An illustration of the clinical course and therapeutic problems is shown in the following case history.

Case history. A 60-year-old white man developed severe anterior chest pain 65 hours before entering the hospital. When seen at home by his physician, 3 hours before hospitalization, his blood pressure was found to be 110/68 mm. Hg, and his heart rate was 90 per minute. Shortly before entering the hospital he suddenly became weak, and, on admission, was found to be cold, clammy, pale, and perspiring, with a blood pressure of 62/? mm. Hg (Fig. 3). A regular cardiac rhythm with a rate of 88 per minute was present; no murmurs or gallop sounds were heard. The heart sounds were faint. The lungs were clear, without râles. Electrocardiographic studies gave findings consistent with a recent posterior myocardial infarction, plus signs of an old anteroseptal myocardial infarction. Normal sinus rhythm was present.

He was given 8 mg. of levarterenol bitartrate in a liter of 5 per cent glucose, by intravenous infusion. His blood pressure rose to normal levels; however, during the first 6 hours of his hospital stay he did not secrete any urine. Subsequently, his output of urine was satisfactory. On the second morning of his hospital stay he developed signs of congestive failure, with râles in the lung bases, and distention of the veins in the neck. At this time he was given Cedilanid, 1.2 mg. intravenously, and subsequently was given digoxin orally as required. The infusion of levarterenol and glucose was continued for 64 hours until midway in the sixth day, at which time it was discontinued. The patient's subsequent hospital course was smooth, and his convalescence uneventful.

COMMENT. This patient was admitted in deep shock, and became anuric for several hours. His response to vasopressor therapy was satisfactory, although he subsequently developed congestive failure. The prolonged administration of l-norepinephrine was required, as well as the use of digitalis. These measures gradually resulted in a return of his hemodynamic state toward normal, with eventual recovery.

FATAL SHOCK. In the group of patient who succumbed to shock, it was frequently difficult to elevate the blood pressure to adequate levels, even with the use of high concentrations of vasopressor substances. These patients as a group often exhibited continued signs of shock (such as sweating, cyanosis, weakness, pallor, and mental confusion), even when the level of blood pressure was maintained adequately by vasopressor substances. There was a high incidence of congestive heart failure with pulmonary edema in this group, necessitating the frequent employment of digitalis glycosides. Their output of urine was generally inadequate, oliguria was common, and anuria also was frequently seen. The patients in the group of fatalities revealed physical signs (such as very small volume pulse) compatible with a profound fall in

cardiac output, as well as with an inability of the homeostatic vasoconstrictor mechanisms to maintain adequate blood pressure and coronary flow. Some of the patients of this group also exhibited marked elevations in the serum glutamic oxalacetic transaminase level. Severe elevations in the transaminase levels have been ascribed in part to the effect of shock upon the liver, rather than to cardiac damage alone.[24] A typical case history of a patient who succumbed to shock is outlined below.

Case history. Two days prior to admission this 59-year-old white woman developed anterior chest pain, associated with nausea and vomiting. This pain persisted in mild degree during the succeeding 2 days. Early on the morning of her admission to the hospital she suddenly became weak, restless, and cold and clammy. At that time she was examined at home by her physician, who found her blood pressure to be 70/? mm. Hg. On admission to the hospital she was in deep shock, and was sweating, pale, and semiresponsive. Her heart rate was found to be 120 (Fig. 4) per minute with a regular rhythm. The heart sounds were weak, but no murmurs were heard. The lungs were clear, without râles.

Difficulty was encountered in finding a vein for infusion, and she was given methoxamine hydrochloride, 20 mg. intramuscularly, without response. Her blood pressure shortly became unobtainable. A polyethylene catheter was inserted into the femoral vein, and levarterenol was given in a concentration of 24 mg. per liter. This was subsequently increased to 32 mg. per liter. A brief pressor response was obtained, but it was not sustained. Within 6 hours after she had been admitted, moist râles appeared in both lung fields and spread extensively; dyspnea was evident. She was digitalized with 1.6 mg. of Cedilanid, given by slow intravenous administration, and oxygen was given continuously. Clinical signs of shock persisted throughout her hospital stay, and she lapsed into coma. One hundred cubic centimeters of concentrated urine were obtained by catheterization 2 hours after her admission. Subsequently, the patient became anuric, and remained so until death.

Postmortem examination was obtained and revealed thrombotic occlusion of the anterior descending branch of the left coronary artery, with a recent anteroseptal infarction of the left ventricle. Pulmonary edema was also present, with associated hydrothorax.

COMMENT. This patient exhibited the features of severe shock, with a progressive downhill course and failure of response to large amounts of l-norepinephrine, plus rapid digitalization. She became anuric, comatose, and developed severe congestive failure with pulmonary edema. No satisfactory or sustained pressor reaction was obtained, the clinical signs of shock were never relieved, and adequate homeostasis was never achieved.

Prognostic differentiation — surviving and fatal cases

Various clinical features of the survivors and of those who succumbed are listed in Table III.

Response to therapy. In estimating the prognosis, one of the most dependable indications of survival was the promptness and

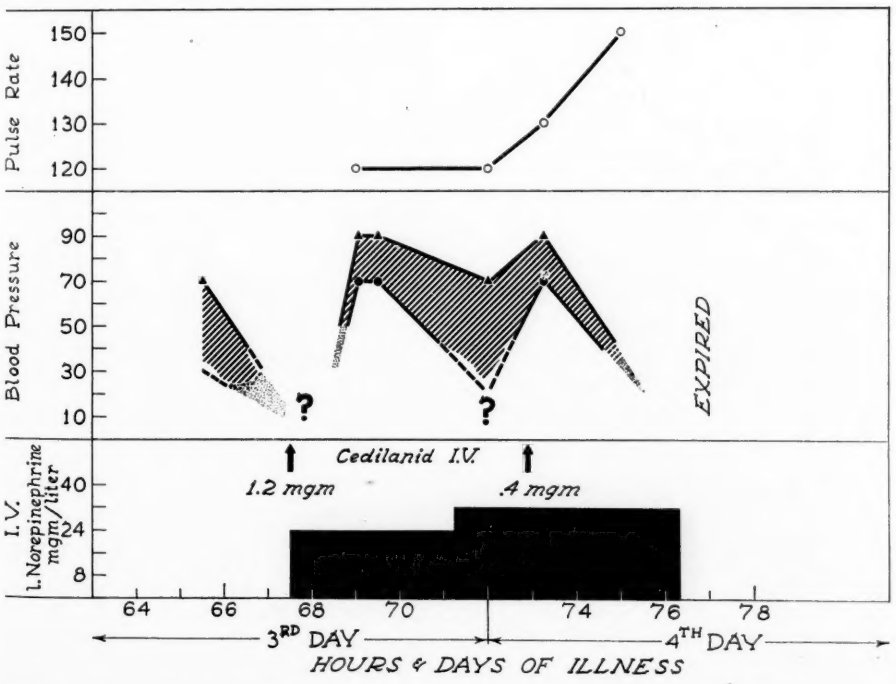

Fig. 4. Fifty-nine-year-old woman. Fatal shock after myocardial infarction (see text).

Table III. *Clinical features of surviving and fatal cases*

	Survivors	*Fatal cases*
Number of patients	29	25
Adequate pressor response	29 Patients (100%)	18 Patients (72%)
Output of urine (after therapy)	Adequate	Oliguria or anuria
Vasopressor administration rate	Good response to low rate	High rate needed
Time delay before treatment (average)	0.7 hr.	2.6 hr.
Arrhythmias	6 Patients (21%)	10 Patients (40%)
Congestive failure	11 Patients (38%)	16 Patients (64%)
Average age	58.6 yr.	64.5 yr.
Average transaminase level	125 SGOT units (16 patients)	182 SGOT units (12 patients)

completeness with which shock was reversed by treatment, especially with the use of adequate vasopressor therapy. A prompt return of blood pressure to normal levels, accompanied by the disappearance of clinical signs of shock, was generally a favorable omen. The contrary was also generally true. However, some patients survived after the prolonged use of antipressor agents. The presence of oliguria or anuria, indicating poor renal perfusion, was likewise a prognostic sign of considerable importance, since patients who remained completely anuric after vasopressor therapy uniformly had a fatal course.

Rate of administration of levarterenol. The rate of administration of levarterenol needed to achieve a pressor effect, as has been noted by others,[8,17,20,25] was a prognostic sign of considerable value. In general, those patients who needed very large amounts of levarterenol per unit of time, to secure an adequate pressor response, generally failed to survive the episode. In the present series the maximum concentration of levarterenol bitartrate employed, with subsequent survival, was 32 mg. per liter; one patient who required this concentration lived. All of the other surviving patients responded to lesser concentrations of levarterenol.

In one instance, 72 mg. of levarterenol bitartrate were given in one liter of solution in an effort to achieve adequate vasopressor effect; this did not result in the patient's survival. Survival has, however, been reported occasionally after the use of high concentrations of l-norepinephrine.[25] Thus, the requisite rate of administration of vasopressor substances needed to produce an elevation in blood pressure was an important factor in an assessment of the prognosis, and the patients in whom a rapid rate of administration of a relatively large amount of levarterenol was needed to maintain their blood pressure generally had a poor outlook.

Duration of shock before therapy. The duration of shock before treatment varied markedly in this series. The shortest duration of shock prior to treatment was less than a quarter of an hour; the longest duration, in a patient whose religious scruples delayed treatment, was 18 hours.

The time elapsed before the institution of adequate treatment was of great importance. In the surviving group (Table IV) the average time before adequate vasopressor therapy was instituted was less than 1 hour. In the patients who succumbed to shock the average period before treatment was instituted was 2.6 hours. None of the patients in whom treatment for shock was delayed for over 2½ hours survived. By contrast, the great majority of patients who survived received adequate vasopressor therapy within an hour after the onset of shock. When treatment was begun within 2 hours (Table V), the mortality rate was 40 per cent. In those patients in whom treatment was delayed more than 2 hours the mortality rate was 78 per cent. Sampson and Zipser,[20] Miller and Moser,[17] Griffith and associates,[3] and other investigators[26,27] have also reported a sharp rise in the mortality rate when

Table IV. *Time elapsed before vasopressor therapy for shock was begun (54 cases)*

	Survivors	*Fatal cases*
Number of patients	29	25
Total hours before treatment was begun	19.7	65.5
Average hours before treatment was begun	.7	2.6

Table V. *Mortality rate compared with interval before vasopressor therapy was begun (54 cases)*

	Number of patients	*Survivors*	*Deaths*	*Mortality (%)*
Treatment begun within 2 hr.	45	27	18	40
Treatment begun after 2 hr.	9	2	7	78

there is a delay in the treatment of shock after myocardial infarction.

Arrhythmias. Severe arrhythmias were encountered more frequently in the patients who died (Table III). Thus, 40 per cent of the patients who succumbed to shock developed arrhythmias, whereas only 21 per cent of the patients who survived developed arrhythmias. Complete heart block and ventricular tachycardia both were prognostic signs of grave nature, and, when they persisted for any considerable period of time, were associated with a high mortality rate in this series of patients.

Congestive failure. Congestive failure occurred more frequently (Table III) in those patients who succumbed to shock. Moreover, when it developed, it was accompanied by a higher rate of mortality—59.2 per cent—than that occurring in those patients who did not develop failure, and in whom the mortality rate was found to be 29.6 per cent (Table VI). Thus, congestive failure, when it developed, was often an indication of grave cardiac insufficiency, and when severe, frequently indicated a serious prognosis. It should be noted, however, that some of the patients who developed congestive failure improved after the institution of adequate digitalis therapy, and survived the episode of shock.

Age. It will be seen with reference to Table I that, although 2 patients in the ninth decade survived the episodes of shock, in general the mortality rate rose in the older age groups. Thus, in the fifth decade the mortality was only 20 per cent, whereas in the eighth decade the mortality had risen to 85 per cent. Age, therefore, would seem to be a pertinent factor in an estimation of the outlook for survival.

Treatment

The mounting mortality rate with the passage of time clearly indicated that shock after myocardial infarction should be treated as a medical emergency, with the least possible delay. Symptomatic therapy, such as the use of analgesics, elevation of the foot of the bed, and oxygen, relieved the premonitory shock promptly in some patients. However, in all cases of persistent shock, vasoconstrictor agents were utilized. Previous reports have shown that the use of transfusions and intravenous fluids, including plasma, does not decrease the mortality rate of shock when employed alone.[2,3] In the group of 54 patients who received adequate therapy, levarterenol was given in 48 cases. Metaraminol was given alone in 4 patients. In one patient, phenylephrine was given by slow intravenous infusion over a period of 18½ hours, with satisfactory elevation of the blood pressure and the survival of the patient. In 10 patients, generally prior to beginning l-norepinephrine or metaraminol, mephentermine was given for variable periods of time. L-norepinephrine was the vasopressor agent of choice, and was administered in the concentration and at the rate needed to effect an adequate vasopressor response. In this series the longest duration of treatment with l-norepinephrine following which the patient survived was 113½ hours.

In an attempt to detect shock promptly, the blood pressure and heart rate were often determined at intervals of an hour or two, for the first 2 or 3 days of hospitalization. If shock persisted for more than a short period, levarterenol bitartrate was generally given intravenously, beginning with a concentration of 8 to 16 mg. per 1,000 c.c. of solution. The rate of administration was governed by the blood pres-

Table VI. *Congestive failure in shock after myocardial infarction (54 cases)*

	Number of patients	*Deaths*	*Mortality (%)*
Congestive failure present	27	16	59.2
Congestive failure absent	27	8	29.6

Table VII. *Shock after myocardial infarction. Results of digitalization (54 cases)*

Digitalis	*Total cases*	*Survivors*	*Deaths*	*Mortality (%)*
Digitalized	34	16	18	53
Not digitalized	20	13	7	35

sure and varied from 6 to as many as 40 or more drops per minute. This concentration was increased as needed to produce an adequate rise in blood pressure. It appeared preferable to keep the blood pressure in the neighborhood of 100 to 110 mm. Hg systolic. Marked elevations in blood pressure were avoided, in order to prevent increased cardiac work in the presence of a damaged myocardium. When shock was severe, and prolonged administration of vasopressor agents necessary, use was made of a polyethylene catheter passed into the deep veins. No definite evidence of aggravation of congestive failure due to vasopressor therapy was observed.

Since many of the patients with severe shock developed congestive heart failure, digitalis was frequently administered. Reference to Table VII reveals that the mortality was higher in patients who received digitalis. Usually in actual practice, however, digitalis was given in the most severe cases, and, as would be expected, these patient had a high fatality rate. However, digitalis was often useful in controlling the symptoms of congestive failure, and probably was responsible for aiding in the recovery of many of the surviving patients. The intravenous administration of Cedilanid was usually employed in this series, although rapid oral digitalization was occasionally used.

The development of arrhythmias occasionally complicated the shock state; these included complete heart block, auricular flutter and fibrillation, and episodes of tachycardia, both of auricular and ventricular origin. When persistent, unless quickly treated by appropriate means, these arrhythmias led to further deterioration of the cardiac status and to deepening of shock. In one instance, ventricular fibrillation developed in a patient in severe shock. Defibrillation by means of electroshock was successfully accomplished (utilizing an external defibrillator), with subsequent spontaneous return to normal sinus rhythm and survival of the patient. Oscilloscopic monitoring of the cardiac rhythm was occasionally utilized during critical stages of shock, and was of aid in evaluating and planning therapy.

Discussion

Several studies have clarified the hemodynamics of patients with shock after myocardial infarction. Freis[28] reported a profound reduction in stroke volume and cardiac index associated with the development of tachycardia, and usually accompanied by an increase in peripheral resistance. He postulated that neurogenic reflexes of a compensatory nature produced the tachycardia and the increase in peripheral resistance.

Gilbert and his co-workers,[29] Smith and associates,[30] and Gammill and his co-workers[31] have corroborated Freis' findings of a profound fall in cardiac output and stroke volume after cardiogenic shock. Lee[32] has also confirmed the profound fall in cardiac output in patients with shock after myocardial infarction. These studies have also generally shown an increase in peripheral resistance, although, in some instances, peripheral resistance failed to rise. Agress, Binder and co-workers[8,33-35] have indicated that when a compensatory rise in total peripheral resistance fails to occur, shock may develop after myocardial infarction. These latter workers have suggested the possibility of an inhibitory reflex, arising in the damaged myocardium, which prevents the rise in peripheral resistance in the presence of a diminished cardiac output.

Corday and associates[36] have pointed out the importance of diminished arterial blood pressure in decreasing coronary flow, and the reversibility of this effect when l-norepinephrine is employed. They have also shown that shock produces a selective fall in blood flow in areas of poor coronary circulation, resulting in a lack of contractility of the heart muscle in these regions, in experimental animals.[37] Restoration of blood pressure to normal resulted in a

return of normal contractility of these areas of heart muscle.

The classic experiments of Wiggers[38] in animals indicate that irreversible circulatory failure may occur when hemorrhagic shock is prolonged for an extensive period. Savranoglu and associates[39] have shown that after an hour sustained tissue anoxia in animals seems to produce myocardial damage of irreversible degree. In addition, Calvia and his co-workers[40] have shown that the decreased availability of myocardial oxygen and the decrease in effective coronary flow which occur in shock can be reversed readily by restoration of blood pressures to normal with levarterenol. Corroboration of the effects of persistent shock in these animal studies is seen in the present series of patients in whom prolonged delay in the institution of therapy appeared to be lethal in almost all cases.

It thus appears from the results of the present study, as well as from the above-cited laboratory investigations, that a critical time factor exists, which must not be exceeded if survival is to be expected when shock occurs after a myocardial infarction. If inadequate coronary flow persists for a prolonged period of time, irreparable weakening of the myocardium occurs. Prompt abolition of shock and the maintenance of adequate perfusion pressure and coronary flow are therefore of paramount importance if the patient is to survive the episode of myocardial infarction.

Summary and conclusions

1. In 714 patients with proved acute myocardial infarction, shock developed in 58 cases, an incidence of 8 per cent. The characteristic clinical features of this group of 58 patients was reviewed and various factors affecting the prognosis were evaluated.

2. The majority of cases of shock after acute myocardial infarction developed within the first 72 hours.

3. In 54 patients who received adequate treatment with vasopressor substances the mortality rate was 46 per cent. This was a definite improvement over previously reported series treated by nonspecific measures, in which the mortality rates ranged from 70 to above 90 per cent.

4. Premonitory shock, which was transitory in nature, developed in 36 per cent of the patients, and was later followed by persistent shock.

5. Among the factors affecting the prognosis, the duration of shock before treatment was of crucial importance. When adequate vasopressor therapy was begun within 2 hours, the mortality rate was 40 per cent; when therapy was delayed over 2 hours, the mortality rate mounted to 78 per cent. No patient in this series survived when treatment was delayed over 2½ hours.

6. Lack of prompt response to vasopressor therapy, severe congestive failure, the development of persistent arrhythmias, and anuria were all prognostic signs of grave importance.

7. The importance of early recognition and prompt treatment of shock after myocardial infarction was evident.

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The vectorcardiogram in interatrial septal defect and persistent atrioventricular canal

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There are many problems concerning interatrial septal defect (IASD) and persistent atrioventricular canal (PAVC) which still have to be clarified from the vectorcardiographic point of view, in spite of a number of papers published on the subject.[1-6]

In the present study, we will consider some problems which, in our opinion, are of great importance. These are: (1) whether there is any relationship between the rotation and morphology of the QRS loop in the horizontal plane (HP) and the right ventricular systolic pressure (RVSP); (2) whether in the case of IASD there is any conduction disturbance in the right bundle branch; and (3) the eventual value of the vectorcardiogram (VCG) in the differential diagnosis between IASD (of the ostium secundum type), PAVC, and other congenital defects.

Material and methods

Material. The VCG of 45 patients with defects of the interatrial septum were analyzed. On the basis of the diagnosis of the anomaly the cases were classified into three groups. Group I: IASD of the ostium secundum type—34 cases; among these were 8 cases of partial anomalous drainage of the pulmonary veins into the right auricle. Group II: IASD of the ostium secundum type associated with rheumatic alteration of the mitral valve—2 cases; one of these was a case of pure mitral stenosis and the other was a case of double lesion with marked predominance of insufficiency. Group III: PAVC—9 cases; 5 were the total form of PAVC, and 4 were the partial form.

The diagnosis of the cardiopathy was based on clinical, roentgenologic, electrocardiographic, and hemodynamic data and was confirmed by operation under direct vision in all of the patients, except 2 in Group III. In these 2 patients the diagnosis of the malformation was confirmed by necropsy.

The patients ranged in age from 5 to 46 years. Thirty were females and fifteen were males.

Methods. The VCG were registered using Grishman's cube system and a Sanborn Viso-Scope apparatus. The vectorcardiographic loop was modulated and interrupted 400 times per second.

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Table I. *Rotation of QRSsÊ in each plane*

Group	Horizontal plane			Frontal plane			Sagittal plane		
	CW	"8"	CCW	CW	"8"	CCW	CW	"8"	CCW
I	20	12	2	25	9	–	–	18	16
II	2	—	–	2	–	–	–	—	2
III	2	3	4	—	2	7	3	6	—

CW: Clockwise. "8": Figure of eight. CCW: Counterclockwise.

Results

The rotation of the QRSsÊ in each plane is summarized in Table I.

Group I. Among the 20 cases (Fig. 1) in which there was a QRSsÊ with clockwise rotation in the HP throughout the extent of the loop, 17 of them showed predominance of the portion directed to the left, and only 3 showed predominance of the portion directed forward and to the right (Fig. 2). The 12 cases with a figure-of-eight inscription in the HP showed a clockwise-rotated terminal portion directed forward and to the right (Fig. 3). The 2 cases with counterclockwise rotation throughout the extent of the QRS loop showed a great preterminal and terminal delay directed forward and to the right (Fig. 4). Besides these 2 cases, delays were registered in 18 others, among which there were 8 of the preterminal and terminal type (Fig. 1), 9 exclusively terminal, and 1 exclusively preterminal. Seven cases showed terminal portions directed upward, rightward, and forward; these, however, were of small magnitude. Nevertheless, in 2 cases (6 per cent) the QRSsÊ was totally directed upward, forward, and to the right (Fig. 5).

The TsÊ was oriented to the left in all of the cases, and backward and downward in 19 cases. In general, the backward and leftward deviation was not too marked (Fig. 1).

Relating the morphology and rotation of the QRSsÊ to the systolic pressure in the right ventricle, with the exception of the 2 cases in which there was counterclockwise rotation throughout the extent of the QRS loop in the HP, we found that: (1) in cases in which the portion of the loop which was directed forward and rightward was of small magnitude, the mean RVSP was 41.5 mm. Hg, varying from 30 to 46 mm. Hg in 19 cases and from 50 to 55 mm. Hg in the other 5 cases; and (2) in cases in which there was important deviation of the loop forward and to the right (8 cases) the RVSP ranged from 42 to 69 mm. Hg (average, 58 mm. Hg).

Group II. The first case in this group, a case of IASD associated with mitral stenosis, also showed predominance of the leftward-directed portion over the forward and rightward-directed portion that had a clear preterminal delay. In the second case (Fig. 6), a case of IASD associated with predominant mitral insufficiency, the HP inscription showed a slightly delayed preterminal appendix with a counterclockwise rotation and a predominant forward and rightward-directed portion.

The TsÊ was oriented backward and to the left in both cases. The RVSP was 50 and 60 mm. Hg, respectively.

Group III. The QRSsÊ was oriented upward, forward, and to the right in all cases of PAVC. In the 4 cases in which the rotation was counterclockwise in the HP an important forward and rightward-directed portion with preterminal and terminal delay (Fig. 7) was registered. The 2 cases with clockwise rotation in the HP did not show any delay in the inscription of the loop (Fig. 8). In the other 3 cases in which there was a figure-of-eight inscription in the HP (Fig. 9), preterminal and terminal delay was registered in 2 cases and only preterminal delay in the third. It is interesting to note that in the frontal plane (FP) the rotation was counterclockwise in 7 cases, and that in the sagittal plane (SP) it was a figure-of-eight inscription in 6 cases and showed complex morphology in all cases.

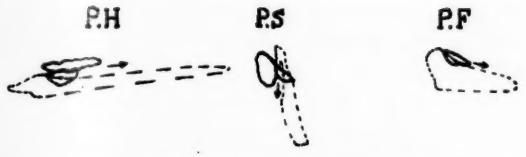

Fig. *1.* IASD of the ostium secundum type. Clockwise rotation in the horizontal plane, with a RVSP of 35 mm. Hg. Terminal delay is seen in the three planes.

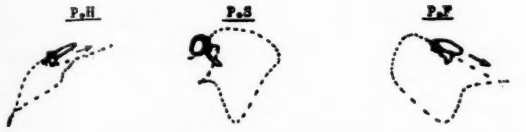

Fig. *2.* IASD of the ostium secundum type. An important portion of the QRSsÊ loop is directed forward and to the right. The RVSP is 60 mm. Hg.

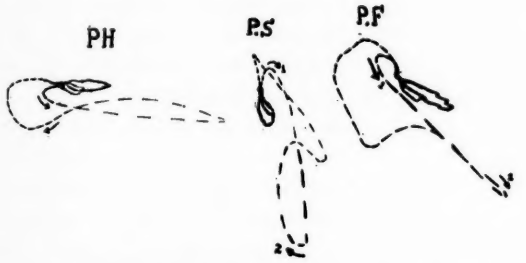

Fig. *3.* IASD of the ostium secundum type. A figure-of-eight inscription is seen in the horizontal plane, and terminal delay is observed in both the horizontal and sagittal planes.

The TsÊ was oriented downward, backward, and to the left in all the cases.

The RVSP ranged from 30 to 100 mm. Hg. In the 2 cases with clockwise rotation throughout the extent of the loop in the HP the pressure was 70 and 83 mm. Hg, respectively.

Comments

Group I. In 20 cases of IASD of the ostium secundum type the diagnosis of right ventricular overload was made on the basis of the clockwise rotation in the HP[1] (Fig. 1). In the other 12 cases in which the rotation was not clockwise throughout the extent of the loop (Fig. 3) the configuration of the loop in the HP, and especially the forward and rightward orientation of the terminal portion with clockwise rotation, allowed us to establish the diagnosis of initial right ventricular overload.[7,8] In reality, this configuration of the QRS loop in the HP was observed in cases of regression of right ventricular enlargement in cardiopathies for which operation was performed under direct vision, preceding the normalization of the vectorcardiographic curve.[9]

Relating the morphology and rotation of the QRS loop in the HP with the RVSP, we found that there seems to be a certain relationship between the levels of pressure and the magnitude of the forward and rightward-directed portion of the loop, as long as the conduction disturbance is not very important.

In our experience,[10] an important fact was the difference in behavior of the QRSsÊ in the HP in cases of IASD (volume overload) and in cases of pure pulmonary stenosis (barrier overload). Thus, in cases of IASD with slightly increased or even

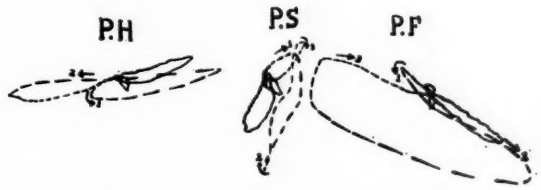

Fig. *4.* IASD of the ostium secundum type. VCG of the complete RBBB type: counterclockwise rotation in the horizontal plane, with preterminal and terminal delay directed forward and to the right.

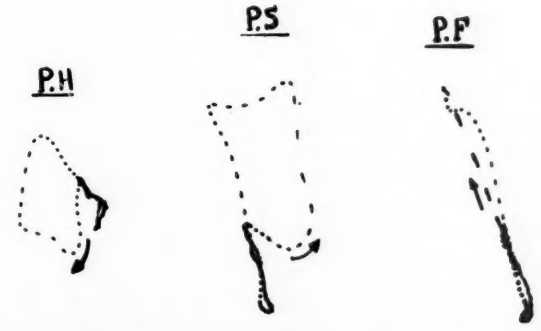

Fig. *5.* IASD of the ostium secundum type. The QRSsÊ is directed upward and to the right completely. Note the predominantly clockwise rotation in the frontal plane.

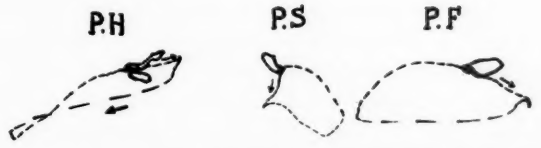

Fig. *6.* IASD of the ostium secundum type associated with double mitral lesion. Observe the lack of the upward-directed portion of the QRS loop.

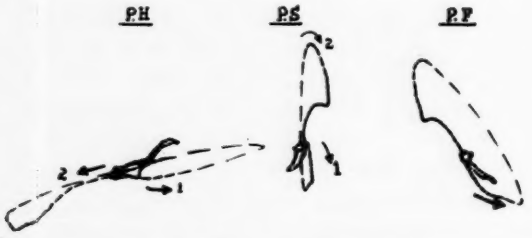

Fig. 7. Persistent atrioventricular canal. The VCG is of the complete RBBB type, with upward and rightward orientation of the QRS loop. Counterclockwise rotation in the horizontal plane.

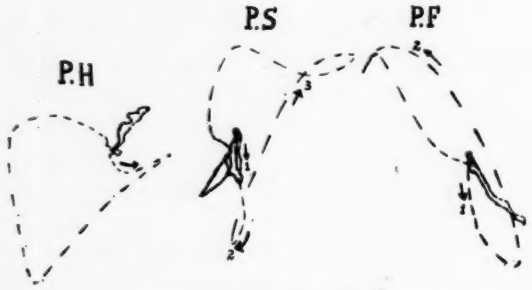

Fig. 8. Persistent atrioventricular canal. Absence of delay in the QRS loop. Clockwise rotation in the horizontal plane and counterclockwise rotation in the frontal plane.

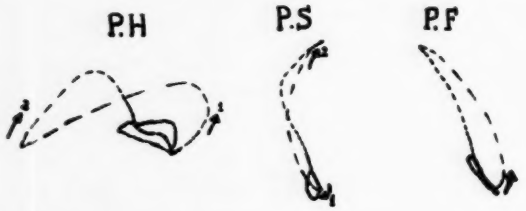

Fig. 9. Persistent atrioventricular canal. The QRS loop has a figure-of-eight inscription in the horizontal plane, and a counterclockwise rotation in the frontal plane.

normal RVSP, clockwise rotation in the HP was registered in the majority of instances (60 per cent), whereas a figure-of-eight inscription was observed in 35 per cent of the cases. Among our cases of pulmonary stenosis, clockwise rotation in the HP was registered only in cases in which the RVSP was above 65 mm. Hg, whereas the rotation was always counterclockwise in cases in which the RVSP ranged from 45 to 60 mm. Hg. For this reason, we are of the opinion that one should not correlate the various elements of the ECG and the VCG with the RVSP when the different types of cardiopathies that may overload the right ventricle are being considered together in a single group; instead, each anomaly should be analyzed separately.

It is probable that this difference in the vectorcardiographic behavior between the right ventricular overload of IASD and that of pure pulmonary stenosis can be related, at least in part, to the more frequent association of conduction disturbance in cases of volume overload (IASD). Thus, the diastolic overload of the right ventricle would almost always be accompanied by either stretching of the fibers of the right bundle branch (incomplete or complete block)[11] or, at least, a certain dilatation of the right basal portions, and, therefore, an almost customary delay in the conduction of stimuli in the Purkinje system of this region.[12] Some other authors admit that the conduction disturbance in the right bundle branch is of congenital origin in the case of this cardiopathy.[13]

Our viewpoint is that in the majority of cases of IASD there is really a conduction disturbance in the right and anterior zones that is clearly demonstrated by the vectorcardiogram in about 55 per cent of our cases (Figs. 1 and 3). However, it is *very difficult to tell on the basis of our present knowledge* whether the delay is due to conduction disturbance in the right bundle branch or in the basal Purkinje system.

The vectorcardiographic diagnosis of complete right bundle branch block (RBBB) (Fig. 4) was made in 2 cases; both showed counterclockwise rotation in the HP and evident preterminal and terminal delay directed forward and to the right.

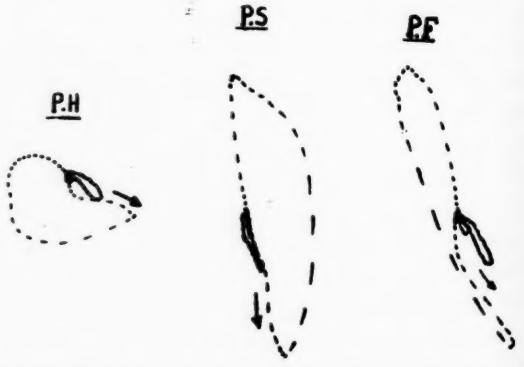

Fig. 10. IVSD with upward and rightward orientation of the QRSsÊ. Clockwise rotation in the horizontal and frontal planes.

As can be seen, this type of bundle branch block is relatively rare (present in 6 per cent of the cases), and some authors, such as Burch,[14] after electrocardiographic studies do not admit the existence of complete RBBB in IASD. These authors believe that the QRS complexes with duration of 0.12 second or greater are representative of right ventricular hypertrophy, occurring mainly in aged patients. Our 2 patients with complete RBBB were 12 and 32 years of age, respectively. Both patients underwent operation, but in spite of the normalization of the heart area and right ventricular pressure no vectorcardiographic modifications were registered in posterior studies.[9]

The persistence of the morphology of complete RBBB in cases of IASD which had been completely corrected by operation suggests definite conduction disturbance, probably of congenital origin.

Group II. The VCG of the case in which there was association of IASD with mitral stenosis was similar to the VCG of the cases of Group I. In the second patient who had IASD associated with predominant mitral insufficiency the VCG showed a delayed preterminal portion with counterclockwise rotation in the HP, suggesting a conduction disturbance in the right branch accompanying right ventricular overload; these facts might have hindered the appearance of the signs of left ventricular enlargement. It should be noted that in this case the VCG did not show upward and rightward orientation as in PAVC.

Group III. No vectorcardiographic differences were observed between the partial and total forms of PAVC. Complete RBBB was registered more frequently in PAVC than in IASD, being present in 4 cases (45 per cent) (Fig. 7). In the other 5 cases there was evidence of right ventricular overload associated with left ventricular overload, and in 3 cases, intraventricular conduction disturbance was registered (Fig. 9).

In all of our cases the most constant vectorcardiographic finding was the marked deviation of the QRSsÊ loop upward and to the right, even in cases with high RVSP (100 mm. Hg); this fact has already been observed by several authors.[3,4,15] This peculiar orientation of the QRS loop (upward) has been related to left ventricular overload, which is anatomically true in the case of PAVC, and to the hypertrophy of the basal portions, in which case a possibly smaller quantity of Purkinje fibers might contribute to a delay in the progress of the stimulus. In our opinion, it is very probable that these two factors are of importance, since all of our cases showed marked left ventricular enlargement on x-ray examination, and 7 of our cases showed rather evident delays in the vectorcardiogram.

The vectorcardiographic pattern of PAVC. The analysis of our material allows us to establish that in the majority of cases of PAVC the vectorcardiograms tend to show a uniform behavior characterized by the following elements: (1) marked deviation of the QRSsÊ loop upward and to the right (100 per cent of the cases); (2) presence of the morphology of complete RBBB (45 per cent of the cases); (3) figure-of-eight rotation in the sagittal plane, with complex morphology (65 per cent of the cases); (4) counterclockwise rotation in the frontal plane (80 per cent of the cases); (5) counterclockwise or figure-of-eight rotation in the horizontal plane (80 per cent of the cases).

Differential diagnosis between PAVC and other cardiopathies with similar vectorcardiographic behavior. According to our experience, vectorcardiographic features (QRSsÊ loop oriented upward and to the right) similar to those observed in PAVC have been found in the following cardiopathies: chronic Chagas' myocarditis, myocardiosclerosis, and, less frequently, congenital anomalies. Among the latter we have to consider IASD of the septum secundum type in 7.5 per cent (Fig. 5), and pure interventricular septal defect (IVSD) in 20 per cent of our cases (Fig. 10). It is our opinion that even in cases of IASD in which the QRS loop is directed upward and to the right some elements may facilitate the differential diagnosis with PAVC. These elements are: (1) Conduction disturbance of the complete RBBB type is rare in IASD. (2) The rotation of the QRS loop in the frontal plane was clockwise or figure-of-eight in the great majority of cases of IASD. (3) The rotation in the horizontal plane was clockwise in all cases of IASD.

Summary

Thirty-six cases of interatrial septal defect (IASD) of the septum secundum type (2 of these cases showed association of rheumatic alteration of the mitral valve) and 9 cases of persistent atrioventricular canal (PAVC) were studied from the vectorcardiographic point of view.

Attention is drawn to the following points: (1) clockwise rotation in the horizontal plane in IASD of the septum secundum type, in spite of normal or slightly elevated right ventricular systolic pressure; (2) high incidence of intraventricular conduction disturbance (55 per cent of the cases of IASD); (3) persistence of the morphology of complete right bundle branch block (RBBB) in the VCG in cases of isolated IASD after surgical correction of the defect and normalization of the cardiac area and of pressure in the right ventricle; (4) value of the VCG in the diagnosis of PAVC; and (5) vectorcardiographic data for the differential diagnosis between PAVC and isolated IASD (of the septum secundum type) and interventricular septal defect (IVSD), with the QRSsÊ loop oriented upward and to the right.

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Differentiation of massive pericardial effusion from cardiac dilatation using I^{131} albumin

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The differentiation of massive pericardial effusion from cardiac dilatation is frequently difficult, even when a thorough diagnostic study including routine roentgen techniques is carried out. To illustrate this problem, x-ray films from 6 patients with enlargement of the cardiac shadow are illustrated in Fig. 1. Films numbered *1*, *2*, and *3* are from patients in whom cardiac dilatation was the principal lesion, whereas films numbered *4*, *5*, and *6* are from patients with massive pericardial effusion. The close similarity of films 1 and 4, 2 and 5, and 3 and 6 is apparent. Angiocardiography will permit ready differentiation, but this procedure is not without risk.[1,2] Cardiac catheterization and the injection of carbon dioxide as a gas contrast medium have also been utilized to make this distinction.[3-5] Recently, a radioisotope technique for the estimation of the intracardiac blood volume has been described.[6] This is based on the use of intravenously injected I^{131} albumin which remains in the vascular system long enough to become essentially equally distributed in the circulating blood. The blood volume of the organ could be calculated if its total radioactivity could be measured accurately and compared to the radioactivity of a unit volume of circulating blood. In the case of the heart, the volume of blood in its chambers is large compared to that in the coronary vascular bed. Therefore, this approach measures essentially intracavitary blood. By comparing the intracardiac blood volume calculated by this method to the area of the cardiac shadow, it is possible to detect a large pericardial effusion. In the presence of pericardial effusion, the intracardiac blood volume is normal and the heart shadow is greatly enlarged. Cardiac dilatation, on the other hand, produces a large intracavitary volume and a proportionately large cardiac shadow.

Materials and methods

Eight hospitalized patients with large cardiac shadows on the teleoroentgenogram were studied by the same technique described previously in 41 patients.[6] Of the 49 patients, 7 had pericardial effusion confirmed by pericardiocentesis or at autopsy. Their diagnoses were: tuberculous pericarditis, 2; metastatic carcinoma to

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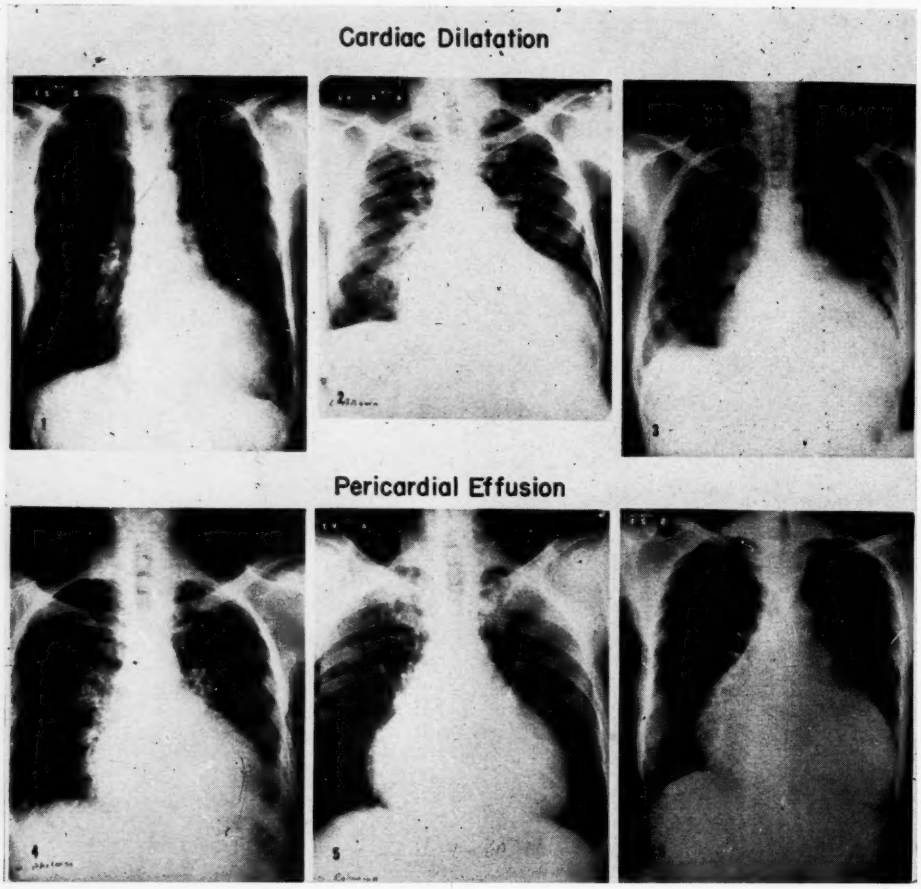

Fig. *1.* Comparison of cardiac shadows in cardiac dilatation and pericardial effusion.

pericardium, 2; disseminated lupus erythematosus, 1; chronic glomerulonephritis, 1; and mediastinitis with pericarditis, 1. The diagnosis of pericardial effusion was made clinically but not confirmed in an additional patient with lupus erythematosus. During treatment with corticosteroids the heart shadow of this patient rapidly returned to normal. This patient is represented by circle *A* in Fig. 2.

The dimensions of the heart shadow were determined fluoroscopically in each patient. The cardiophrenic angles and two points immediately below the pulmonary artery on opposite borders of the cardiac shadow were projected to the anterior chest wall. A four-sided paper pattern was constructed corresponding to these four points. Lead shielding was placed around the margins of the paper pattern to prevent detection of radioactivity in the lungs and great vessels, in so far as possible. Corrections were made in the size of this pattern so that it was reduced in size to allow for the fact that shielding was placed between the crystal and the heart rather than around the edges of the heart. A heavily shielded 2-by-2-inch cylindrical NaI crystal was placed 25 cm. from the anterior chest wall over the center of the heart. Scintillation pulses corresponding to energies below 0.15 Mev. were eliminated by a spectrometer. The precordial radioactivity was recorded after allowing 10 minutes to elapse after the injection of 50 to 100 μc of I^{131} albumin into an arm vein. Venous blood was collected into a tube containing dry heparin at this time. From this sample the hematocrit was determined by centrifugation at 2,000 RCF. The hematocrit was corrected for 3 per cent trapped intercellular plasma. Plasma radioactivity was measured as previously described.[7] Radioactivity of whole blood was calculated using the corrected hematocrit.

An I^{131} albumin standard was counted within a tissue phantom made of masonite to determine the mean counting rate of 1

μc of I^{131} albumin within the normal human heart. This counting rate was then related to the counting rate of 1 μc of I^{131} albumin obtained with the Geiger-Müller tube employed in measurements of whole blood. For these particular counters the Geiger-Müller tube recorded 166 times as many counts per microcurie of I^{131} albumin as did the precordial probe. Thus, the intracardiac blood volume is equal to:

$$\frac{\text{Precordial radioactivity (cpm)}}{\text{Whole blood radioactivity (cpm/ml.)}} \times 166.$$

The factor 166 is based on normal-sized hearts. In 4 of the patients with enlarged hearts, individual calibration factors were obtained. The resulting figures were 145, 153, 154, and 168. These differences were believed to be minor. The factor 166 was used for calculation in all patients.

Results and interpretations

The intracardiac blood volume of all patients was plotted against the area of the precordium monitored (Fig. 2). There is an approximate linear relationship between the area monitored and the calculated intracardiac blood volume in the normal subjects and in patients with heart disease. Of 8 patients known to have pericardial effusion, 5 had a normal intracardiac blood volume of less than 800 ml. and a large heart shadow. Of the other 3, 2 were found to have cardiac dilatation at autopsy (*B* and *C*). In one of these (*C*), cardiac dilatation was the predominant lesion; the pericardial effusion totaled approximately 100 ml. The third subject (*D*) survived, so that the presence or absence of cardiac dilatation could not be determined by pathologic examination.

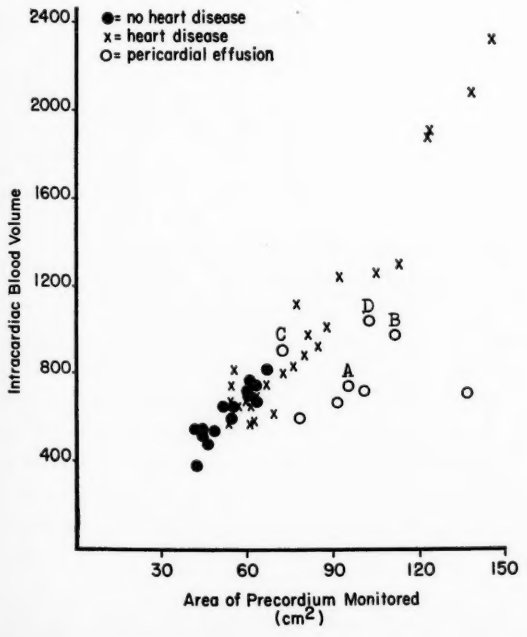

Fig. 2. Relationship of intracardiac blood volume to area of cardiac silhouette.

Discussion

Errors inherent in the measurement of the intracardiac blood volume by the present technique have been previously discussed.[6] Accuracy might be significantly improved by using more satisfactory methods for outlining the cardiac shadow with shielding and by determining calibration factors for the individual patients. Scintograms of the heart may also be used to determine the presence of pericardial effusion,[8] but the apparatus necessary is more complex than that required for the estimation of the intracardiac blood volume. The experience to date is not sufficient to establish the reliability of present techniques, but the results clearly indicate that this is a sound approach to the clinical diagnosis of pericardial effusion.

Summary

1. An isotope technique for the measurement of intracardiac blood volume has been used to detect massive pericardial effusion.

2. An outstanding feature of this procedure is its simple and innocuous nature.

3. In 5 patients with pericardial effusion and normal hearts the cardiac shadows were enlarged whereas the intracardiac blood volumes were normal.

4. The results indicate that this is a sound approach to the clinical diagnosis of pericardial effusion.

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Disability absenteeism of industrial workers with myocardial infarcts

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The physician who wishes to rehabilitate patients who have recovered satisfactorily after myocardial infarction must recognize a number of deterrents. Among these are fear that the individual will have another attack for which the employer may be held liable, and concern that the cardiac employee cannot work effectively, and that he will experience high and costly sickness absenteeism.

The administration of compensation benefits for workers who experience subsequent attacks is a complex process which often involves courts, commissions, and customs wherein the testimony and opinions of the individual practitioner of cardiology seemingly carry little weight. For removal of this obstacle to cardiac rehabilitation, legal and socioeconomic reforms would seem to take precedence over strictly medical advances.

On the other hand, the effectiveness on the job of cardiac workers who are placed in a suitable assignment has been demonstrated so widely and overwhelmingly that the productivity of such employees is no longer of major concern. In this study, data which pertain to the absenteeism experience of industrial workers with proved myocardial infarcts are presented. Such information, which heretofore has received scant attention, may be helpful to physicians in discussing return-to-work situations with patients and employers alike.

Method

The 100 subjects whose records form the basis of this report were selected from current or recent lists of permanently partially disabled employees identified in the total population of 7,500 workers of a large oil refinery and petro-chemical plant. The two criteria required for inclusion in the study were: (1) the worker must have a diagnosis of healed myocardial infarction established beyond reasonable doubt, after which, (2) he must have resumed work for a period of at least a year. (Data collected on subjects whose period of work was 6 to 12 months did not differ significantly from the findings to be presented; however, subjects with less than a year of work experience after infarction were excluded in order to avoid the possible criticism that the period of observation at work was too short.) All have been effective workers on the job, since they were included in an organized program for the selective placement of handicapped workers which entailed periodic review by both physician and supervisor.[1] The average age of the study group was 50 years, as compared to 45 years for the entire worker population.

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Complete information as to the number of absences from work due to disability, the duration of each absence, and the clinical reason for each absence was collected for each of the 100 subjects. The survey period began with the patient's return to work after an initial myocardial infarction and ended June 30, 1960. Seven subjects in the study group became totally and permanently incapacitated for work, and 3 died. For these individuals the survey period ended on the last day on which they worked.

Some patients experienced subsequent infarcts and again resumed work for a year or more. The periods of absence from the job due to later attacks are included in the analysis. Only five infarcts in this series were "silent" or unrecognized in the acute stage. These were discovered, usually at routine periodic examination, when stable electrocardiographic patterns typical of healed infarction were found on individuals whose previous tracings were normal. Such findings were not associated with periods of disability.

The absenteeism experience of the 100 workers with proved myocardial infarcts is compared with data for the whole refinery population, derived in a similar manner for those years in which most of the cardiac cases were analyzed. Each period of absence is measured in calendar days, and rates are calculated according to the procedure recommended by the American Medical Association Committee on Medical Care for Industrial Workers.[2]

Other matters concerned with heart disease and employment have been excluded as irrelevant to the study of absenteeism.

Results

The 100 subjects of this study had an average of 4.7 years (range: 1 to 17 years) at work after the initial episode of myocardial infarction. Thus, 470 man-years of work experience are included in the survey. Ten workers subsequently developed a second infarct, and 2 patients had a third. In all, 112 infarctions were recognized in the subjects during the study.

Disability absenteeism rates for the cardiac workers are compared with rates for all refinery workers in Table I. The worker with a healed infarct was absent 10.0 calendar days annually because of sickness or injury (disability rate), as compared to an average of 9.9 days for all refinery workers. The annual number of absences per employee (frequency rate) for the cardiac group was 1.2, and for all workers, 1.1. The average duration of absence (severity rate) was 8.3 days for the study group, and 8.9 days for the whole worker population.

Only 2.7 of the 10 days of absence each year by the cardiac worker were the result of cardiovascular disease. The major types of cardiovascular disabilities occurring in the 100 subjects are shown in Table II. Chest pain due to angina, coronary insufficiency, or myocardial infarction accounted for two to three times as many days of disability as did either myocardial failure or other conditions (arrhythmias, strokes, hypertension, peripheral vascular disease, and time away from the job for observation and regulation of medication). The frequency rate for cardiovascular absences was 0.16, and the severity rate was 17 days.

Analysis of absenteeism by age group (Table III) reveals variation in cardiovascular absences from 2.2 days per year for the 50-54 age group to 4.7 days for the 45-49 age group. The increase in noncardiovascular absences in workers in the 60-64 age group was caused by a number of prolonged periods of disability involving operations.

Table IV compares the absenteeism experience of salaried employees and wage earners. The salaried group was composed of 16 supervisory and technical and 26 clerical workers, 42 in number, with an observed work experience of 210 man-years. The wage earners consisted of 39 skilled and 19 unskilled employees, a total of 58 with 260 man-years at work after infarction. Cardiovascular absences for the salaried workers averaged 1 day per worker annually, as compared to 4 days for the wage earner. All types of disabilities for the salaried employee amounted to 6.7 days yearly, about half the number of days (12.7) lost by the wage employee. Corresponding disability rates for these groups in the entire population were 6.1 and 11.6. In addition to disability and frequency rates, the duration of absence for an episode of acute myocardial infarction is

Table I. *Disability absenteeism experience*

Employee group	*Disability rate (days/employee/yr.)*	*Frequency rate (absences/employee/yr.)*	*Severity rate (days/absence)*
Workers with healed infarcts (100 employees)	10.0	1.2	8.3
All refinery workers (7,500 employees)	9.9	1.1	8.9

Table II. *Cardiovascular causes of disability for work in 100 employees with healed infarcts*

Cause of absence	*Disability rate (days/employee/yr.)*	*Frequency rate (absences/employee/yr.)*	*Severity rate (days/absence)*
Chest pain	1.5	0.07	21
Myocardial failure	0.5	0.02	25
Other (arrhythmias, etc.)	0.7	0.07	10
All cardiovascular	2.7	0.16	17

Table III. *Absenteeism experience by age group*

Age group (yr.)	*Number of workers*	*Number of infarcts*	*Work experience (man-years)*	*Disability rate (days/employee/yr.)*		
				Cardiovascular	*Other*	*Total*
40–44	13	14	52	2.3	5.6	7.9
45–49	14	16	63	4.7	5.2	9.9
50–54	18	18	97	2.2	4.2	6.4
55–59	31	36	136	2.8	5.4	8.2
60–64	24	28	122	3.4	13.9	17.3

Table IV. *Absenteeism of salaried employees and wage earners*

Employee group	*100 Workers with healed myocardial infarcts*							*All refinery workers*
	Disability rate (days/employee/yr.)			*Frequency rate (absences/employee/yr.)*			*Average days lost with acute infarcts*	*Disability rate (days/employee/yr.)*
	Cardiovascular	*Other*	*Total*	*Cardiovascular*	*Other*	*Total*		
Salaried (42 workers)	1.0	5.7	6.7	0.12	1.06	1.18	93	6.1
Wage (58 workers)	4.1	8.6	12.7	0.18	1.08	1.26	109	11.6

shown. This was 93 days for the salaried worker and 109 days for the wage earner; the combined average was 102 days.

Discussion

These data suggest that patients with myocardial infarction who are able to return to work in a suitable assignment do not have high disability absenteeism. The 100 subjects, with a total observed experience of 470 man-years, on resuming work after an infarction averaged only 10.0 calendar days of disability annually. In comparison, the average for all refinery workers was 9.9 days. The survey group also had surprisingly low frequency rates for disability absences—0.16 for cardiovascular causes and 1.2 for all causes.

These findings are in general agreement with other reports on absenteeism of full-time workers with heart disease of various etiologies. One hundred and eighty-nine workers followed by the Work Classification Unit, Adult Cardiac Clinic of the Third (New York University) Medical Division, Bellevue Hospital, lost an average of approximately 9 days per year.[3] Greer[4] reported an average absenteeism of 13.3 days annually for 45 industrial workers with arteriosclerotic heart disease, compared with 11.3 days for all employees. Neither report described details of the derivation of data upon which conclusions were based.

Wyshak, Snegireff and Law[5] studied absenteeism of workers with various types of heart disease or diabetes in 17 manufacturing plants,[5] and found that employees with coronary heart disease were able to work with little more disability than persons free of heart disease; cardiac workers placed in "light" jobs lost less time than "production" workers.

A previous study from this department also revealed a generally good prognosis for patients who returned to work after cardiovascular absences.[6] Nearly 88 per cent of those who resumed work either continued on the job or retired for nonmedical reasons. In the course of the 3-year observation period, approximately 6 per cent died and another 6 per cent retired for medical reasons. This analysis, based on a large number of cardiovascular absences of all types, differs from the present one which is based on the experience of patient-employees with a specific type of heart disease.

It may appear surprising that the employees of this study who had established heart disease of a serious nature did not lose more time from the job because of disability than did the average worker. It is possible that such employees, having recovered satisfactorily from a life-threatening illness to resume a productive job in industry, are highly motivated to stay on the job and avoid unnecessary absences. Even though higher job motivation may be contributory to the lower absenteeism experience of salaried workers as compared to wage earners, other important factors are the generally better work environment and less physically demanding assignments available to the "white collar" worker.

It deserves re-emphasis that disability absenteeism is affected by many factors, nonmedical as well as medical.[7] For example, it has long been recognized that some periods of apparent "disability" bear a strong relationship to the availability and duration of disability payments. None of the workers who were surveyed was involved in a compensation suit. All were covered by a company benefit plan which provided, in general, full pay for the first 12 weeks of disability, and one-half pay for an additional 40 weeks. Such a plan offers sufficient economic security to generally deter efforts to work when actually disabled, and joint follow-up of each absentee by full-time company physicians and the personal physician tended to minimize unnecessary and unduly prolonged periods of absence.

Summary

Disability absenteeism of 100 subjects who resumed industrial work for an observed 470 man-years after myocardial infarction is reviewed. They experienced 10.0 calendar days of disability per person annually, whereas the average for all workers in the same plant was 9.9 days. Only 2.7 days of absence each year were due to cardiovascular conditions. The cardiac employee had, on the average, 1.2 periods of disability yearly, as compared to 1.1 absence per worker for the whole refinery population. Analysis of absenteeism by age

group revealed no significant trend in the patients studied. Salaried cardiac workers had one fourth as many days of absence for cardiovascular reasons, and one half as many days of disability for all reasons, as did wage earners.

The absenteeism experience of workers with healed myocardial infarcts who resumed work in a suitable job assignment did not differ significantly from that of the whole plant population.

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Marked left axis deviation
Indication of cardiac abnormality

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Left axis deviation is a common electrocardiographic finding, yet opinion as to its significance has varied considerably, ranging from normal variant to definite evidence of cardiac disease. This has been due in large part to a lack of uniformity in definition. It has been considered present by some when the mean QRS axis is no more leftward than +30 degrees. Others have defined it as at least −30 degrees leftward orientation of the axis. It has been pointed out[1-4] that leftward deviation of −30 degrees or more (LAD) is usually associated with cardiac disease. This observation has been minimized by the lax use of the term "left axis deviation" and is often ignored, particularly in an otherwise normal electrocardiogram.

The factors considered to cause left axis deviation have included altered anatomic and electrical position of the heart, emphysema, left bundle branch block, left ventricular hypertrophy, myocardial fibrosis, and unknown factors associated with aging. Left ventricular hypertrophy has been considered to be the most common cause. Grant[4] proposed that LAD is usually due to myocardial fibrosis: either patchy involvement in the distal intraventricular network (parietal block) or more proximally by myocardial infarction (peri-infarction block). He found a wide angle between the mean initial 0.04-second and mean terminal QRS vectors in the latter and thought that, with LAD, an angle that exceeded 100 degrees might be helpful in diagnosing anterolateral myocardial infarction even in the absence of diagnostic Q waves.

Intrigued by Grant's concept and impressed by the frequency with which this electrocardiographic finding has been encountered at the Veterans Administration Hospital, Houston, Texas, we undertook this study.

Methods

The electrocardiograms of all patients who died in this hospital during a 10-year period were surveyed. Of approximately 2,500 patients, 252 were found whose electrocardiograms showed the mean QRS axis to be directed between −30 and −90

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Table I. *Diagnosis of 154 patients at necropsy*

Diagnosis	*Normal QRS duration*		*Prolonged QRS duration*		*Total*
	Emphysema		*Emphysema*		
	With	*Without*	*With*	*Without*	
With myocardial infarction					
Normal mean initial vector	3	6	2	5	16
Abnormal mean initial vector					
Diaphragmatic	3	9	1	5	18
Anterolateral with peri-infarction block	1	5	1	11	18
Otherwise abnormal	3	5	2	5	15
Without myocardial infarction					
Right ventricular hypertrophy	6	0	0	0	6
Valvular disease	0	1	0	3	4
Hypertensive heart disease	2	10	4	4	20
Arteriosclerotic heart disease	13	4	1	3	21
Idiopathic fibrosis	7	5	0	0	12
Miscellaneous	0	2	0	1	3
"No heart disease"	0	3	0	0	3*
Bundle branch block					
Right					
With infarction	0	1	1	1	3
Without infarction	0	0	2	3	5
Left					
With infarction	0	0	3	5	8
Without infarction	0	0	0	2	2

*One additional patient who had no evident heart disease is listed as having right bundle branch block without infarction.

degrees (LAD). Lesser degrees of leftward deviation were not investigated. Ninety-eight patients could not be studied because necropsy was not performed or because the hearts or clinical records could not be examined. The report deals with the other 154 patients.

Mean vectors were determined for the total QRS duration, the initial 0.04 second of the QRS, and for the remainder of the QRS (mean terminal vector). Particular attention was given to the lateral wall of the left ventricle, on both gross and microscopic examination. The weight of the heart was considered to be the most reliable index of left ventricular hypertrophy.

The 154 patients were separated into 2 groups containing those with normal QRS duration (0.09 second or less in the standard limb leads) and those with prolonged QRS duration. The 2 groups were further separated as seen in Table I. The patients with myocardial infarction were categorized according to the direction of the mean initial 0.04-second QRS vector. Good correlation existed between the electrical and anatomic position of the infarction.

The term "anterolateral infarction with peri-infarction block" was used to designate only those cases in which the mean initial 0.04-second QRS vector was directed between +90 and +180 degrees. A diagnosis of arteriosclerotic heart disease included only those patients with angina pectoris or in whom moderate to marked sclerosis of the coronary artery was found at necropsy. A diagnosis of idiopathic myocardial fibrosis applied only to those patients with fibrosis but no clinical evidence of heart disease and no more than minimal sclerosis of the coronary artery. No patient was listed in more than one category. Emphysema was accepted as having existed when such a diagnosis had been made either

Table II. *Diagnosis of 100 living patients with LAD*

Diagnosis	*With clinical heart disease*		*Without clinical heart disease*		*Total*
	LAD only	*LAD plus other ECG abnormality*	*LAD only*	*LAD plus other ECG abnormality*	
With myocardial infarction					
Normal mean initial vector	1	1	—	—	2
Abnormal mean initial vector					
Diaphragmatic	–	2	—	2	4
Anterolateral with peri-infarction block	–	2	—	2	4
Otherwise abnormal	–	4	—	7	11
Without myocardial infarction					
Right ventricular hypertrophy	–	–	—	—	0
Valvular disease	–	3	—	—	3
Hypertensive heart disease	1	4	2	1	8
Arteriosclerotic heart disease	3	7	—	—	10
Idiopathic fibrosis	–	–	—	—	0
Miscellaneous	5	7	—	7	19
"No heart disease"	–	–	21	10	31
Bundle branch block					
Right	–	–	—	3	3
Left	–	3	—	2	5

Table III. *Age by decades of 154 patients at necropsy and of 100 consecutive living patients with LAD*

	Fourth	*Fifth*	*Sixth*	*Seventh*	*Over seventh*	*Total*
Necropsy	4	20	37	69	24	154
Living	4	6	8	59	23	100

clinically or at necropsy. We have some reservations as to the reliability of these criteria for the diagnosis of emphysema.

A series of 100 consecutive living patients with LAD was also studied (Table II). These patients were encountered in a 4-month period, during which time electrocardiograms were recorded on approximately 600 patients. The 2 patients with myocardial infarction and normal mean initial 0.04-second vector had had diagnostic clinical courses and electrocardiograms during previous hospitalizations. "Arteriosclerotic heart disease" was used to designate only those patients with angina pectoris. The miscellaneous group was comprised of 12 patients who had cardiomegaly or heart failure that was not clearly due to the other listed causes, and 7 patients with electrocardiographic changes of left ventricular hypertrophy or strain as the only evidence of cardiac disease.

Results

All of the patients were male. This was attributed to the almost exclusively male population of the hospital. Only 4 patients were younger than 40 years (Table III). One of these had a myocardial infarction, 1 had malignant hypertension, and 2 had idiopathic myocardial fibrosis.

Myocardial infarction was present in 80 of the 154 patients (52 per cent). Of the 136 patients without bundle branch block,

65 had myocardial infarction. Three of the 8 patients with right, and 8 of 10 patients with left, bundle branch block had myocardial infarction. Twenty-six of the 80 patients with myocardial infarction did not have a history of infarction. Eighteen of these 26 patients also had nondiagnostic electrocardiograms, including 1 with right, and 4 with left, bundle branch block.

The 2 patients with left bundle branch block without myocardial infarction had aortic stenosis. Five patients with right bundle branch block did not have myocardial infarction. One patient had angina pectoris, 2 had aortic insufficiency, and 1 had no clinical evidence of cardiac disease but did have a mild increase in heart weight. The fifth patient had no evidence of caridac disease clinically or at necropsy.

There were 69 patients who had neither myocardial infarction nor bundle branch block (Table I). The 6 patients with right ventricular hypertrophy had clinical cor pulmonale. There were 4 patients listed in the valvular disease group. An additional 8 patients had valvular disease, 6 of whom also had myocardial infarction or angina pectoris and 2 of whom had left bundle branch block. Aortic stenosis or insufficiency was present in 11 patients and mitral insufficiency in 1 patient. All patients in the group with idiopathic myocardial fibrosis demonstrated mild fibrosis except 1, in whom it was marked (Table IV). The weights of the heart were normal or only slightly increased (Table V).

In the miscellaneous group, the patient with the prolonged QRS had scleroderma with extensive cardiac and pulmonary involvement. The second patient had recurrent myocarditis of unknown etiology. The third patient had a Grade 2 apical systolic murmur as the only clinical manifestation of heart disease. Necropsy disclosed mild fibrosis and mild increase in the weight of the heart as the only cardiac abnormalities.

Four patients had no evidence of cardiac abnormality, clinically or at necropsy. One was included in the group that had right bundle branch block. One patient had nonspecific T-wave abnormalities, and 1 had prolongation of the Q-T interval. The fourth patient, who died of a progressive chorea of undetermined etiology, was found at necropsy to have extensive fatty infiltration of the myocardium. We were reluctant to attribute the LAD to the infiltration.

Fifty-five patients were thought to have emphysema. The distribution of these patients in each of the diagnostic categories is presented in Table I.

QRS prolongation greater than 0.09 second was present in 65 patients. Seventeen had bundle branch block. Of the patients without bundle branch block, myocardial infarction was present in 32 of 48 patients with prolonged QRS duration, in contrast to 35 of 88 with normal QRS duration. Generally, those with prolongation had greater heart weights. The degree of fibrosis varied widely in those with QRS prolongation, but only 5 had none. Duration of the QRS varied from 0.10 to 0.20 second. Duration exceeding 0.12 second occurred exclusively in those patients with left bundle branch block and in those with anterolateral myocardial infarction and peri-infarction block. No relationship could be demonstrated between the QRS duration and weight of the heart, thickness of the myocardium, or degree of fibrosis.

Heart weight and fibrosis (Tables IV and V) could be correlated with the diagnostic categories, as might be expected: that is, generally greater heart weights in patients with hypertensive and valvular disease and generally more fibrosis in patients with coronary artery disease. Myocardial fibrosis was diffuse, and no particular involvement of the anterolateral wall of the left ventricle was observed.

The vector angle was wide in two categories: (a) patients with anterolateral myocardial infarction with peri-infarction block, by criteria of selection, and (b) patients with right bundle branch block. The vector angle was narrow in those patients with diaphragmatic myocardial infarction and in those with left bundle branch block. With these exceptions, the vector angle could not be correlated with diagnosis, weight of the heart, or extent of fibrosis. Emphysema has been stated to widen the vector angle. If known instances of emphysema were excluded, no correlation could be found between the vector angle and the presence or absence of myocardial infarction.

Table IV. *Degree of myocardial fibrosis in 154 patients at necropsy*

Diagnosis	*Normal QRS duration*				*Prolonged QRS duration*			
	None	*Mild*	*Moderate*	*Marked*	*None*	*Mild*	*Moderate*	*Marked*
With myocardial infarction								
Normal mean initial vector	—	—	—	9	—	—	—	7
Abnormal mean initial vector								
Diaphragmatic	—	—	—	12	—	—	—	6
Anterolateral with peri-infarction block	—	—	—	6	—	—	—	12
Otherwise abnormal	—	—	—	8	—	—	—	7
Without myocardial infarction								
Right ventricular hypertrophy	6	—	—	—	—	—	—	—
Valvular disease	1	—	—	—	—	3	—	—
Hypertensive heart disease	4	7	1	—	2	4	—	2
Arteriosclerotic heart disease	2	6	4	5	1	2	—	1
Idiopathic fibrosis	—	11	—	1	—	—	—	—
Miscellaneous	—	2	—	—	—	—	—	1
"No heart disease"	3	—	—	—	—	—	—	—
Bundle branch block								
Right								
With infarction	—	—	—	1	—	—	—	2
Without infarction	—	—	—	—	2	3	—	—
Left								
With infarction	—	—	—	—	—	—	—	8
Without infarction	—	—	—	—	—	1	—	1

Seventeen of the 154 patients had LAD as the only electrocardiographic abnormality. Four of these had myocardial infarction, 3 of whom had no suggestive clinical history. The fourth patient had a diagnostic clinical course and serial electrocardiograms showing changes of an acute anterior wall infarction which gradually evolved to LAD only. Five patients had arteriosclerotic heart disease, and 1 had hypertensive cardiovascular disease. Six patients had idiopathic myocardial fibrosis. The patient in the "No heart disease" group was the one with marked fatty infiltration.

There were 9 patients with nonspecific T-wave abnormalities and 2 with prolongation of the Q-T interval as the only associated electrocardiographic changes. Five of these had arteriosclerotic heart disease, 1 had hypertensive cardiovascular disease, 3 had idiopathic myocardial fibrosis, and 2 had no evidence of heart disease.

The remainder of the patients demonstrated electrocardiographic evidence of myocardial infarction, left ventricular hypertrophy, "strain," injury, ischemia, or intraventricular conduction defects.

Table II summarizes the clinical data on 100 consecutive living patients with LAD. Six patients had valvular disease, 3 of whom also had myocardial infarction. Aortic stenosis or insufficiency was present in 5 patients, and mitral insufficiency in 1 patient. One patient had cor pulmonale, but also left bundle branch block. The frequency of the diagnostic categories as compared to the first series was as follows: bundle branch block, 8 as compared with 11 per cent; valvular disease, 6 as compared with 8 per cent; hypertensive cardiovascular disease, 8 as compared with 12 per cent; arteriosclerotic heart disease, 10 as compared with 13.5 per cent; myocardial infarction, 21 as compared with 49 per cent; and no heart disease, 31 as compared with 2.6 per cent.

Four of the living patients were younger than 40 years of age. One patient had a myocardial infarction. Three had no evident heart disease, although 1 was known

to have diabetes mellitus of 8 years' duration. The average age of the living patients was slightly greater than that of those in whom necropsy was performed (Table III).

Because of the infrequency of young patients in both series, the electrocardiograms of 100 consecutive patients under 40 years of age were reviewed. LAD was present in 2 patients, one with a previous myocardial infarction and the other with heart failure of undetermined etiology.

Discussion

The results of this study support the experience of others that, with rare exception, left axis deviation of greater than −30 degrees is electrocardiographic evidence of cardiac abnormality. There were only 4 patients (2.6 per cent) of the 154 at necropsy who had no evidence of cardiac abnormality clinically or at necropsy.

This study did not decisively answer the question of whether left ventricular hypertrophy or myocardial fibrosis was the principal etiological factor of LAD. The number of patients without fibrosis (13 per cent) was similar to the number without increase in the weight of the heart (17 per cent). The occurrence of mild fibrosis and mild increase in the weight of the heart was also nearly equal: 24 and 23 per cent. The observation that myocardial infarction was present in 52 per cent of the patients, and unequivocal coronary artery disease in an additional 13 per cent suggested that myocardial fibrosis was the more important factor.

The valvular disease group was interesting not only because of its small size, but because of the type of lesion encountered: aortic stenosis or insufficiency in 11. These lesions usually cause left ventricular hypertrophy. They also are associated commonly with disturbances in coronary circulation. Indeed, 5 of the patients had either angina pectoris or myocardial infarction. The single instance of mitral disease was as-

Table V. *Heart weights of 154 patients at necropsy*

Diagnosis	*Normal QRS duration*				*Prolonged QRS duration*			
	Less than 350 grams	*350 to 450 grams*	*450 to 600 grams*	*Over 600 grams*	*Less than 350 grams*	*350 to 450 grams*	*450 to 600 grams*	*Over 600 grams*
With myocardial infarction								
Normal mean initial vector	3	1	4	1	–	1	5	1
Abnormal mean initial vector								
Diaphragmatic	3	2	5	2	–	2	3	1
Anterolateral with peri-infarction block	3	–	2	1	–	1	8	3
Otherwise abnormal	–	4	1	3	–	2	2	3
Without myocardial infarction								
Right ventricular hypertrophy	4	1	1	–	–	–	–	–
Valvular disease	–	–	1	–	–	3	–	–
Hypertensive heart disease	–	4	8	–	–	1	4	3
Arteriosclerotic heart disease	5	5	5	2	–	–	2	2
Idiopathic fibrosis	5	7	–	–	–	–	–	–
Miscellaneous	–	1	–	1	–	–	–	1
"No heart disease"	3	–	–	–	–	–	–	–
Bundle branch block								
Right								
With infarction	–	–	–	1	–	–	2	–
Without infarction	–	–	–	–	1	2	1	1
Left								
With infarction	–	–	–	–	–	–	5	3
Without infarction	–	–	–	–	–	–	–	2

sociated with marked sclerosis of the coronary artery.

The authors have some reluctance in using the term "emphysema," in view of some of the newer concepts of the disease. However, the usual frame of reference during the survey period implied overdistention of the lungs. Although emphysema was frequent in the subjects of this study, there were only 6 patients in whom it occurred in the absence of either left ventricular fibrosis or hypertrophy. All 6 had marked right ventricular hypertrophy and clinical cor pulmonale. It would seem that emphysema alone rarely causes LAD.

The frequency of reported emphysema was remarkably similar in the patients with bundle branch block (33 per cent), myocardial infarction (24 per cent), and in those with QRS prolongation (23 per cent). In the patients with none of these the frequency was 53 per cent. They were characterized by generally smaller heart weights and degrees of fibrosis. This distribution may be simply fortuitous, but introduces another possible mechanism for the production of LAD: mild left ventricular fibrosis or hypertrophy may cause some leftward deviation of the electrical axis, with emphysema producing further deviation to more than −30 degrees.

Quite consistently in those patients with LAD and emphysema the electrocardiograms were characterized by small voltage in the limb leads and lateral precordial leads.

The angle between the mean initial 0.04-second and mean terminal QRS vectors was found to be of little value in predicting the presence of myocardial infarction.

The number of patients with left bundle branch block and LAD was too small to have statistical significance; however, it was of interest that 8 of 10 had myocardial infarction. Right bundle branch block might be expected to result in LAD, yet only 1 of 8 patients evidenced no cardiac abnormality.

The series of 100 consecutive living patients was quite similar to the group of 154 patients in whom necropsy was performed, in age distribution and in frequency of occurrence of all diagnostic categories, with the notable exceptions of the group with myocardial infarction and that with no heart disease. This discrepancy was probably more apparent than real had the true occurrence of occult myocardial infarction, sclerosis of the coronary artery, and idiopathic myocardial fibrosis been obtainable. Such an assumption seems reasonable in view of the observation that approximately 30 per cent of the patients in whom myocardial infarction was found at necropsy had a negative history, and slightly more than half of these had electrocardiograms which were not diagnostic of myocardial infarction. Also of significance was the fact that 26 of the 31 patients with no apparent heart disease were 60 years of age or older.

A review of the electrocardiograms of 100 consecutive patients under 40 years of age revealed only 2 with LAD. One patient had had a myocardial infarction, and the other had heart failure of undetermined etiology.

No conclusions were drawn of the significance of LAD with reference to prognosis or cardiac functional capacity.

Summary

The electrocardiograms of 154 patients with left axis deviation of the QRS of between −30 and −90 degrees (LAD) were correlated with the findings clinically and at necropsy. Only 4 patients (2.6 per cent) did not have cardiac abnormality, even though in 17 patients the electrocardiograms were normal except for the left axis deviation (LAD). Myocardial infarction was present in 52 per cent of the patients, and unequivocal coronary artery disease in an additional 13 per cent. The angle between the mean initial 0.04-second and mean terminal QRS vectors was of little value in predicting the presence of myocardial infarction. Emphysema was thought to have only a contributory role in producing LAD. The data on 100 consecutive living patients with LAD and on 100 consecutive living patients under 40 years of age were interpreted as affording additional support to the conclusion that LAD, with rare exception, is electrocardiographic evidence of cardiac abnormality.

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Coronary heart disease and hypertension among Jews immigrated to Israel from the Atlas Mountain region of North Africa

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Investigations of the prevalence of coronary heart disease and hypertension as carried out in many countries have dealt mostly with populations that had been natives of their respective countries for many generations. The diversity of population groups in Israel provides opportunities for such epidemiological research, but, in addition, the factor of change in environment by migration may have to be taken into account.

Research on coronary disease in this country has revealed, on the one hand, that it is comparatively rare among Oriental Jews, particularly the Yemenites,[1,2] but, on the other hand, that, together with a rising mean level of cholesterol in the blood, its incidence seems to increase with prolonged stay under the living conditions of Israel, even in immigrant groups previously almost immune to the disease.[3-6]

It seemed of interest to determine the prevalence of coronary heart disease and hypertension in a group of Jews who had recently immigrated to this country from the Atlas Mountain region of North Africa, since almost all of them had exchanged a primitive environment for the atmosphere of a more advanced country. Furthermore, such a stock-taking enquiry may facilitate future research undertaken to deal with the changes possibly evoked by such new and rather revolutionary conditions.

The place chosen for this investigation was Asatah, a settlement in the Northern Negev, where about 3,200 people, mostly derived from the region mentioned, were housed at the time of immigration in 1957.

These people are of Mediterranean stock; this fact has also been borne out by a simultaneous blood-group study.[7] They are usually of medium body size and build. A minority derive from the island of Gjerba, located in continuation of the Atlas territory in the Bay of Tunisia; in most features the people from Gjerba resemble the majority group described. They were mostly craftsmen or peddlers in their native countries (Morocco, Tunisia); their economic and living standard apparently had been very low. At present, they are engaged part time in farming or road building, mostly as unskilled laborers. Their families are of large size, and their living conditions here also are mostly poor.

Up to the time of this study, in the

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summer 1959, they had not yet been well integrated into the social framework of this country, and many had not yet even partly adopted the language of this country. It seemed that their psychologic adjustment to the new environment was equally poor, a situation by no means eased by their relative isolation and concentration among themselves.

The following investigation has been carried out in order to establish to what extent coronary disease and hypertensive vascular disease are prevalent among these Atlas Jews.

Material and methods

Both men and women, the great majority of whom were over the age of 30 years, have been examined. Many of them were patients with minor injuries or ailments who applied to the local Sick Fund Clinic, of which two of us have been in charge in subsequent turns (Y. A. and B. K.); others who were waiting for relatives to be taken care of or who were applying to the nearby labor exchange were invited to take part in this study.

A short history, mainly as to cardiovascular complaints, was taken. A physical examination was performed, with particular attention to cardiac findings, such as: enlargement of the heart, accentuation of the second aortic sound, arrhythmias, and signs of congestive heart failure. A series of blood pressure readings were taken with the subjects in the supine position until the values became stable; these final readings were recorded and used for evaluation.

One hundred and six individuals in whom such casual but repeated blood pressure readings had been obtained were re-examined several months later; the subjects were recalled at random with the purpose of evaluating the significance of such one-time measurements.

In a number of individuals, electrocardiograms and samples of blood (103 and 134 cases, respectively) were taken; this number was determined by the degree of cooperation of the people examined as well as a certain limitation of facilities. The selection of the individuals from whom blood or an electrocardiogram, or both, were to be taken was determined by purely practical considerations (presence of an additional worker of the team, shipping facilities, etc.), so that these examinations can be considered as samples taken at random. After being refrigerated the samples of blood were sent to Jerusalem within, at most, 48 hours for analysis. Blood cholesterol and levels of uric acid were determined. Cholesterol was determined according to Keys and Anderson's modification of Abel's method.[8] Uric acid was determined according to Hepler and Stosskopf[9]; by means of this method, 100 normal adults showed a mean of 3.9 ± 0.57 mg. per cent, and only 3 per cent had values above 5 mg. per cent.[10]

Blood from the samples collected was also used for a study of the blood-group distribution in this community.[7] In addition, a food survey was conducted at the

Table I. *Age distribution of the individuals examined (Atlas Jews)*

Age group (years)	*Males*	*Females*	*Total*
Less than 30	17	28	45
31–40	13	32	45
41–50	28	26	54
51–60	34	19	53
61–70	32	2	34
Over 70	2	1	3
Total	126	108	234

Table II. *Mean cholesterol values in various age groups (Atlas Jews)*

Age group (years)	*Males*		*Females*	
	Mean (mg. %)	*Number of individuals examined*	*Mean (mg. %)*	*Number of individuals examined*
Less than 30	154.4	5	157.2	9
31–40	161.4	9	159.5	20
41–50	155.9	17	163.4	14
51–60	177.0	21	186.1	9
61–70	170.1	28	——	—
Over 70	——	2	——	—
Total		82		52 (134)
Mean cholesterol of total	167.8 ± 38.2		165 ± 32	

Table III. *Findings in the nine abnormal electrocardiograms*

Case number	*Sex*	*Age (yr.)*	*Blood pressure (mm. Hg)*	*Clinical remarks*	*Electrocardiographic findings*
24.	M	57	135/80	—	Low voltage, T_1 isoelectric, T_{AVL} low voltage, left axis deviation
28.	F	47	120/80	—	Horizontal heart, low voltage of T_1, aV_L
56.	M	52	160/100	Rough systolic murmur over Erb's point	Horizontal heart, pronounced left ventricular strain pattern
72.	M	68	135/80	Pulmonary emphysema	T_{AVL} voltage, T_1 flat, Q in aV_L
143.	F	38	130/85	Soft systolic murmur over aorta	Significant Q in aV_L but no other electrocardiographic abnormalities
165.	M	62	180/120	Accentuated second aortic sound	Ventricular extrasystoles
192.	M	74	185/85	Left ventricle enlarged	Symmetrical inversion of T_1, T_{AVL}, $T_{V3,6}$; Q in aV_L old anterolateral infarct
208.	M	65	200/130	Left ventricle enlarged	Left bundle branch block
233.	M	66	170/100	Pulmonary emphysema	Horizontal heart, low voltage of T_1, significant Q and high take off of S-T in aV_L, supraventricular extrasystoles

same time. Both studies will be reported upon separately.[11] However, it may be mentioned here that the daily intake of fat was found to be between 50 and 60 Gm.

When an unexpectedly high prevalence of hypertension was discovered, analyses of urine were made and 24-hour samples of urine were taken in a number of individuals in whom proper cooperation could be obtained, for determination of sodium chloride excretion (flame photometer).

Results

One hundred and thirty men and 106 women, 236 individuals in all, were examined. Table I shows their age distribution. The average age of the men was 50.6 years; that of the women was 38.5 years.

The mean age of the 82 men in whom cholesterol and levels of blood uric acid were determined was 53 years; the mean blood cholesterol value was 167.8 ± 38.2 mg. per cent (range from 72 to 261 mg. per cent). The mean level of blood uric acid was 4.67 ± 0.96 mg. per cent (range from 1.71 to 6.93 mg. per cent).

The mean age of the 52 women thus examined was 39.1 years. The mean blood cholesterol was 165 ± 32 mg. per cent (range from 99 to 226 mg. per cent). The mean level of blood uric acid was 3.33 ± 0.04 mg. per cent (range from 1.56 to 5.42 mg. per cent). Table II shows the mean cholesterol values for both sexes according to age groups.

Figs. 1-4 show the systolic and diastolic blood pressure measurements for the men and women examined. Out of the 236 people studied, 52 individuals (22 per cent) —34 men (26 per cent) and 18 women (16.9 per cent)— had diastolic blood pressures of 95 mm. Hg or more. Consequently, according to common standards, 22 per cent of all the individuals examined have to be considered to be hypertensive. If 90 mm. Hg is taken as the lower limit of hypertension, then 45 men and 34 women—33 per cent of all the individuals—have to be regarded as hypertensive individuals.

Table III reviews the electrocardiographic findings which may be considered as abnormal; in 3 cases (Nos. 72, 192, 233) the presence of ischemic heart disease is indicated. The three individuals concerned are over 65 years of age.

Discussion

The findings encountered in this population group can be summarized as follows. The mean blood cholesterol values of men (167.8 mg. per cent) and women (165 mg. per cent) are low in comparison with those of many Western populations and are close to what has been found in more primitive populations in Africa,[12] India,[13] or in new immigrant Yemenites[3-6,14] and

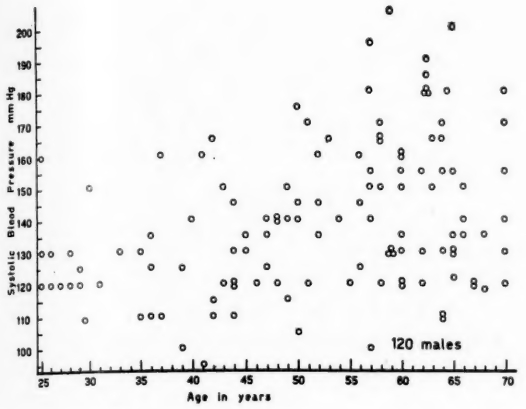

Fig. *1.* Systolic blood pressure values of 120 males studied in this investigation.

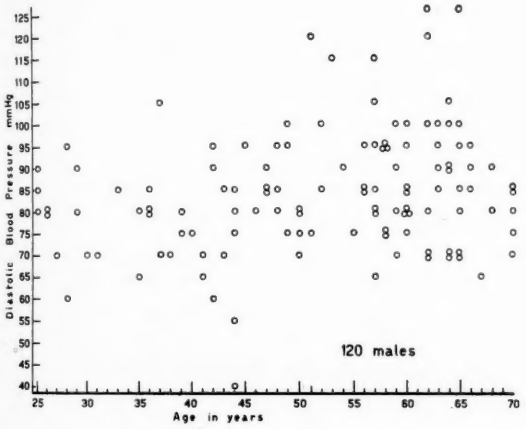

Fig. *2.* Diastolic blood pressure values of 120 males studied in this investigation.

in Jews from Cochin[15] in this country. A trend of the values to rise with age seems to be absent in our group. The highest cholesterol level observed in this series was in a 64-year-old hypertensive man (262 mg. per cent).

The mean blood uric acid levels of 4.67 mg. per cent in males and 3.33 mg. per cent in females seem to be neither unusually low or high. But it should be noted here that so far there seem to be no available figures derived from population or group surveys which would indicate the prevalence of hyperuricemia, nor are there data for mean blood uric acid levels of populations, apart from a rather high mean value of 5.03 ± 1.12 mg. per cent for men and 4.05 ± 0.89 mg. per cent for women recently obtained by us in an investigation of the Cochin Jews.[15] We[16] have previously expressed the opinion, as have others,[17,18] that there seems to be a relationship between an increased level of uric acid and the occurrence of coronary heart disease. Therefore, we have so far included such determinations in surveys designed to study the causes of coronary disease, and we intend to include them in the future.

Coronary heart disease. The determination of the presence and prevalence of coronary heart disease in a given group of individuals can at best be an estimate. This estimate has to be based on the electrocardiographic evidence of myocardial infarction or cardiac ischemia; it has to rely on the experience and observations of the examining physicians, and has to take into account the number of cases of sudden deaths which have occurred under the highly suspect clinical picture of coronary

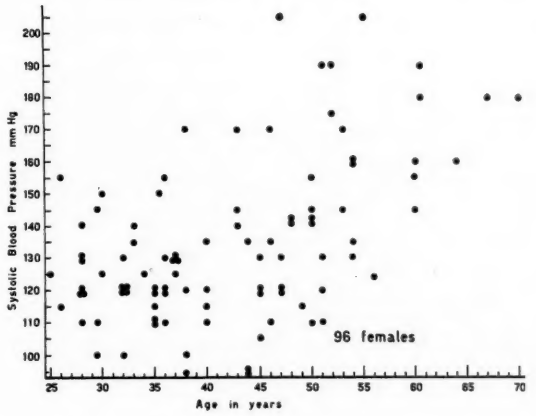

Fig. *3.* Systolic blood pressure values of 96 females studied in this investigation.

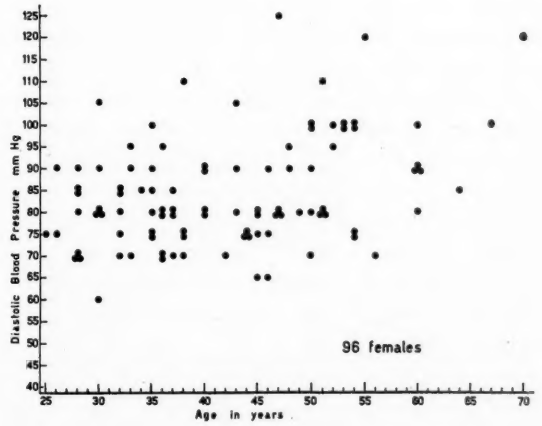

Fig. *4.* Diastolic blood pressure values of 96 females studied in this investigation.

occlusion. Extensive autopsy data—although rarely available—will be most valuable. The finding of a low mean blood cholesterol in a population is today regarded by many as presumptive evidence of a low incidence of the disease in question, whatever the mechanism of such a low level may be. Whether a low mean level of uric acid justifies the same conclusion cannot yet be stated.

In the light of these considerations the evidence at hand should then be examined.

Two of us (Y. A. and B. K.), during a 2-year period in which we were the only physicians serving, in turn, this population, have observed only two men who presented a clinical picture of myocardial infarction. Both died. Otherwise the two of us have not been called upon to see such a case nor have we heard of one in this community, for the medical care of which we were responsible. Among the many patients who have applied to the clinic, only one presented a clear history of anginal pain. This individual suffered from syphilis of the aorta. Among the 9 electrocardiograms which showed any significant abnormalities, one indicated clearly a past infarct of the heart; two others exhibited Q waves in Lead aV_L and changes of the S-T interval in the same lead.

When these scant observations and findings are taken together—possibly with the low mean level of blood cholesterol—the conclusion then becomes justified that coronary heart disease is infrequent among the population group examined.

Hypertension. Although the distribution curve of blood pressure measurements shows a bimodal shape, and therefore suggests the existence of two types of "populations," normotensive and hypertensive subjects, the present material does not seem adequate to enter into the controversy[19,20] whether hypertensive blood pressure has to be considered as a continuation of normal blood pressure or whether it bears the characteristics of an a priori different state. At any rate, there are good reasons to assume that there is no single figure for diastolic blood pressure which will separate hypertensive from normal levels. We therefore report our blood pressure measurements in Figs. 1-4, so that these data can be independently evaluated, with everyone using his own criteria as to what value or values discriminate between normal and high values. Certainly, to say that a certain pressure reading is the one that separates the normal from the elevated is at present impossible.

Accepting with a slight modification the recommendation of the World Health Organization's subcommittee dealing with cardiovascular epidemiology,[21] we consider that all individuals with a diastolic pressure of 95 mm. Hg or above are hypertensive. This appears to be the more justified since, according to impressions gained from previous work,[22] Oriental Jews, when normal, seem to have comparatively low blood pressures. Consequently, 22 per cent of the individuals examined here have to be regarded as hypertensive. If 90 mm. Hg were considered as the artificial line of separation, the unusually high figure of 33 per cent would represent the number of hypertensive individuals.

Even a 22 per cent prevalence of hypertension in a group of people over 30 years of age represents a conspicuously high figure. Therefore, it was considered necessary to take repeated measurements as outlined above (see Methods).

An attempt was made to evaluate the reliability of a one-time determination of blood pressure as described above, testing whether such a determination gives adequate information about the normotensive versus hypertensive state of a given individual. The series of double measurements in 106 individuals who were recalled at random enabled us to examine these data by MacNemar's test for significance.[23] Accordingly, the difference in number of hypertensive individuals was found to be not significantly different as determined on the basis of one as against two examinations in the random group examined. The number of conflicts between measurements was not above the expected figure. It appears that we do face a true increase in the number of hypertensive individuals.

Such a high percentage of individuals with elevated arterial pressure calls for an explanation. Many people who belong to the community examined have told us that they regularly eat a great deal of salt; this seem to hold true for their group in general. An enquiry conducted in their

homes as well as in their food stores and at the clinic tends to confirm these statements. In addition, 21 individuals, who were chosen according to their willingness to cooperate, were found to excrete from 8.75 to 21 Gm. of sodium chloride in 24 hours (mean, 13.9 Gm.). These examinations were carried out in winter in order to obtain samples uninfluenced by excretion of sodium chloride in the sweat. These values seem rather high—16 men excreted more than 10 Gm. of sodium chloride per day, and 7 among them excreted more than 15 Gm.—though not exceedingly so.

A large series of urine analyses as well as clinical experience among this group of people deny an unusual incidence of pyelonephritis as a source of hypertension.

To approach the problem from an entirely different angle, it may be stated that these Moroccan and Tunisian communities have recently undergone great social changes which require considerable adaptation on the part of the individual. Of rural or semiurban origin in a part of their country far removed from Western civilization, these people have been transferred into new, competitive, and puzzling surroundings and circumstances. Moreover, a certain breakup of their social patterns and family cohesion seems to have occurred within recent years: previously, the extended family, the isolated rural background, as well as strict adherence to religious tradition had kept these people within their customary, age-old framework. Apparently, this social structure had already been in a process of radical change and dissolution before the recent immigration of these people to Israel.

Impressions and evidence are recently forthcoming which indicate that in certain population groups atherosclerosis may well be dissociated from hypertension. So far, this concerns mostly ethnic groups of African descent. In the British West Indies, for instance, a large incidence of hypertension has been observed—Humphries[24] found that about 40 per cent of the natives of Nassau had a systolic blood pressure of over 150 mm. Hg. Moser[25] found that over 50 per cent of West Indians who were more than 39 years of age had systolic pressures above 150 mm. Hg; about 30 to 40 per cent of all people over 40 years of age had diastolic pressures of 100 mm. Hg or more. Of those people over 40 years of age, 60 to 70 per cent had a diastolic pressure of above 90 mm. Hg. In these Bahaman people the excretion of sodium chloride seemed to be about 12 Gm. per day on an average in a limited study. Moser and his co-workers,[26] in their study of 3,594 Negro subjects in the Bahamas, report that 25 per cent of the males had a blood pressure of 150/90 mm. Hg; for women the figure was 30 per cent. They have recently concluded[27] from their data and those of others that hypertension is frequent among Negroes, wherever they are, and that, to a certain extent, its incidence is independent from the process of "urbanization." Stuart,[28] at a congress held in Jamaica, in April, 1960, again emphasized the high prevalence of hypertension in Jamaica and St. Kitts, but also pointed out that bacilluria, at least in elderly women, was very frequent and might possibly be a partial explanation of this phenomenon by way of causing pyelonephritis. Dr. Dodu,[29] from Ghana, informed us that he has been impressed with the relative rarity of coronary occlusion, at least in the hospital wards, in Accra (Ghana), whereas hypertension seems by no means to be rare in hospital patients there. Corcoran and his co-workers,[30] in a short preliminary report on their investigations among a group of West Indian Negroes, as studied in St. Kitts, West India, speak about the "Negro's predisposition to hypertension," but stress at the same time "the low prevalence of ischemic heart disease." Also in Japan, where in some village populations hypertension reaches a frequency of 30 per cent,[31] as well as in the South African Bantu,[32] hypertension seems to be frequent, whereas ischemic heart disease is rarer than in Europe or in the United States. Schroeder,[33] in a report on his "cardiovascular itinerary" through various Oriental countries, describes hypertension as by no means rare in all locations where he visited.

All the information available so far—including the well-known tendency of the North American Negro to develop hypertensive cardiovascular disease—concerns, by and large, either Negro populations in various locations or the Japanese. So far, the group which is investigated here, Jews

of Mediterranean stock, as their physical make up and their blood-group distribution clearly show, stands isolated among other Mediterranean peoples, as a new group comprised of many individuals with high blood pressure but apparently little affected at present by ischemic heart disease, or at least affected to a much lesser extent than would be expected if this were a European or North American community with so high a prevalence of high blood pressure. The ultimate meaning of a "high" blood pressure reading is whether it is compatible with good health and a normal life expectancy; or, in other words, only such "high" pressures as those that indicate a future state of defective health or shorter life expectancy may be considered to be abnormal. For this reason, only longitudinal studies will clarify whether there is something like a normal range of blood pressure for the human race—of about 55 to 90 mm. Hg diastolic—which is valid for all groups.

Comparison with other groups, multidisciplinary analysis of genetic and environmental determinants, as well as a long-term follow up of the newly immigrated group may elucidate some of the reasons for such an unusually high proportion of individuals with high blood pressure.

Summary

Two hundred and thirty-six adults newly immigrated to Israel from the Atlas Mountain region have been examined for coronary heart disease and hypertension.

The mean blood cholesterol value in men was found to be 167.8 ± 38.2 mg. per cent; in women it was 165 ± 32 mg. per cent. The mean level of blood uric acid in men was 4.67 ± 0.96 mg. per cent; in women it was 3.33 ± 0.04 mg. per cent.

Although coronary heart disease seems to be infrequent among this ethnic group, the number of people with high blood pressure was found to be unduly large: 33 per cent had a diastolic blood pressure of 90 mm. Hg and above; 22 per cent had a diastolic pressure of 95 mm. Hg and above.

Recently, population groups in which the prevalence of hypertension and coronary heart disease are dissociated have been described, i.e., Negroes and Japanese. The group of people of Mediterranean origin reported on here seems to show this same epidemiological phenomenon: coronary heart disease is uncommon, but hypertension is frequent.

We are grateful to the following individuals who helped us in various ways to carry out this investigation: Dr. Shatal, physician in charge of the Negev District, General Labor Sick Fund; Dr. W. W. Czaczkes, of the Laboratory of Clinical Research, Hebrew University Hadassah Medical School, who supervised the laboratory examinations; Dr. Henry Rosenfeld, social anthropologist, Hebrew University, for his advice; Mr. Benjamin Bracha, the office clerk of the Azata Sick Fund Clinic; Miss M. Mioni, the nurse at that clinic, and Miss Ruth Ben Zeev, of Kibbutz Kfar Aza.

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Myocardial infarction treated by early ambulation
Effect of prolonged anticoagulant therapy on the immediate prognosis after discharge from hospital

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In 1956, we published in this Journal a paper on the effect of early ambulation on the results of treatment of myocardial infarction.[1] Since 1952, it has been the general principle in this hospital to permit patients with myocardial infarction to sit up in bed after the symptoms of shock have passed. Bedside toilet privileges have also been allowed at an early stage. In the absence of specific contraindications the patients have begun ambulation, on an average, 2 weeks after infarction—recently, even earlier—and they have been discharged 1 week later. In other respects, the usual treatment has been administered.

In the above-mentioned series of patients treated in 1952-1954, the results were favorable with respect to the absence of complications during hospitalization. Thus, during the first week of ambulation, which we regarded in advance as the most critical period in the early ambulation, there were only 2 sudden deaths and 1 recurrence in our series of 258 patients. However, during the first month after discharge the incidence of complications was relatively high. In the 236 patients followed up, 1 sudden death and 21 new infarcts occurred. Additionally, 8 patients were rehospitalized for chest pain, the cause of which, however, could not be ascribed to a new infarct. The incidence of complications during the first month after discharge from the hospital was high also in comparison to the following 5 months, during which 10 sudden deaths and 10 new infarcts occurred.

In the discussion in our previous paper, we presented two possible explanations for the relatively high incidence of recurrences during the first month after discharge from hospital, suggesting that it was a result either of early ambulation or of discontinuance of anticoagulant therapy on discharge from the hospital. Since 1952, the majority of our patients with myocardial infarction have received phenylindandione as an anticoagulant during hospitalization, but only since 1957 has this treatment been continued after the patients were discharged from the hospital.

To obtain information concerning the effect of anticoagulant therapy on the high incidence of recurrence during the first month after discharge, we have studied the cases of myocardial infarction in this hospital in the latter half of 1957 and during 1958-1959.

Material

During this period a total of 565 patients with confirmed myocardial infarction were admitted to this hospital. During the

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similar period of 1952-1954, the cases totaled 332; thus, the increase was 70 per cent. Although the increase has certainly been influenced to some extent by the increase in population, and possibly by more sensitive diagnostic criteria, it appears from these figures that a real increase has occurred during this time. In the later series, 127 patients, equivalent to 22.5 per cent of the series, died in the hospital before ambulation was begun. The mortality rate in the series of 1952-1954 was 22.4 per cent. Of the other 438 patients, 117 either received no anticoagulant therapy because of, for example, a complicating disease, such as peptic ulcer or hypertension, or the therapy was discontinued after discharge because of a lack of appropriate laboratory facilities or because of poor cooperation by the patient. However, especially in severe cases an attempt was made, despite the difficulties, to continue the treatment at home, at least during the immediate period after discharge. After exclusion of these two groups, 321 patients remained. In these 321, we observed the course of the disease during the first month after they were discharged, and it is this group which form the basis for the following report of results.

We shall first present certain data concerning the series. The figures in parentheses give the corresponding information for the series of 1952-1954.

Female patients numbered 58, or 18.1 per cent of the series (28.7 per cent), and their mean age was 61 (63) years. The mean age of the male patients was 56 (54) years, and that of the whole series was 56 (57) years.

Using the criteria of Schnur,[2] we grouped the patients as follows according to the severity of the disease: pathologic index rate 0-39: 210 patients = 65.4 per cent (60.5 per cent); pathologic index rate 40-79: 88 patients = 27.4 per cent (32.9 per cent); pathologic index rate 80- : 23 patients = 7.2 per cent (6.6 per cent).

On the basis of the electrocardiographic changes the infarct was diagnosed as: anterior, anterolateral, or anteroseptal type in 193 patients, or in 60.2 per cent (60.0 per cent); posterior or posterolateral type in 107 patients, or in 33.3 per cent (29.0 per cent); purely lateral in 7 (5) patients; and purely septal in 2 (10) patients. Determination of the type was not possible in the other 12 (14) patients.

Confinement to bed averaged 12.0 (16.2) days, and the total period of hospitalization was 20.1 (22.6) days.

Complications during ambulation in hospital. Sudden death: In the present series there was 1 (2) case of sudden death; this was in a 58-year-old man who died on the third day of ambulation after hospitalization for 11 days. New myocardial infarction: There were 2 (1) cases of new myocardial infarction; both of the patients recovered. Congestive heart failure: Symptoms of heart failure developed in 10 (5) patients. The symptoms were mild and transient in 9 patients and severe in only 1 patient. Death occurred in the latter patient after 23 days of hospitalization.

Complications during first month after discharge from hospital. Sudden death: There were no cases (1) of sudden death. New myocardial infarction: There were 8 (21) cases of new myocardial infarction, 2 of which were fatal. One of these infarctions occurred in a 55-year-old man who previously had had two infarcts; the final infarct had been very severe. The other fatality occurred in a 71-year-old woman.

In addition, 8 (8) patients were rehospitalized because of chest pain, in connection with which, however, a new infarct could not be diagnosed. The pain could not definitely be ascribed to cardiac origin.

Discussion

Complications occurring in our hospital during ambulation of patients with myocardial infarct were very few in the present series. Although ambulation began, on an average, as early as 12 days after hospitalization and lasted 8 days, there was only 1 sudden death and 2 recurrences. Ten patients developed symptoms of heart failure, which were mild and transitory in 9 patients. Since ambulation in the hospital is the most critical stage of early ambulation, the findings in the present series conform well to our previously expressed opinion that early ambulation of patients with myocardial infarction involves at least no immediate risk.

As was mentioned above, our series of

236 patients in 1952-1954 had relatively numerous recurrences, i.e., 21, during the first month after being discharged from the hospital, in addition to which there was 1 sudden death—a combined incidence of major complications totaling 9.3 per cent. In the present series the number of recurrences dropped to 8, or 2.5 per cent. The difference in the incidence of new infarcts is highly significant ($p < 0.01$).

The composition of the two series corresponds well, as is indicated by the foregoing data. The only noteworthy differences were that ambulation was begun, on the average, 4 days earlier in the present series than in the 1952-1954 series, and that the number of female patients was definitely larger in the latter series. The last-mentioned difference suggests that the increase in the number of myocardial infarcts has evidently been greater among men. Since both of the mentioned differences might be expected to have had an unfavorable effect on the prognosis in the recent series, the difference in the incidence of recurrences cannot be explained on this basis. It appears probable, therefore, that the lower incidence of recurrent infarcts in the new series is due chiefly to continuation of the anticoagulant therapy. Likewise, it seems evident that the relatively high incidence of recurrences during the first months after discharge from the hospital in the series of 1952-1954 was not a result of early ambulation.

Summary

A series of cases reported upon by us earlier in this Journal dealt with the effect of ambulation, which began, on the average, on the sixteenth day of hospitalization, on the results of treatment of myocardial infarction. The results were favorable, except that during the first month after the patients were discharged from the hospital there was a relatively large number of recurrences of infarction (9.3 per cent). Since anticoagulant therapy was discontinued in that previous series at the time the patients were discharged from hospital, we have compared the results with a more recent series from 1957-1959, in which anticoagulant therapy was continued. The series consisted of 321 patients with myocardial infarction. During their ambulation in the hospital, which in these patients was begun, on the average, on the twelfth day of hospitalization, only 1 sudden death and 2 recurrences of infarction were reported; during the first month after the patients were discharged from the hospital there were 8 new infarctions. Thus, in the new series the number of new infarctions during the first month after discharge from the hospital dropped from 9.3 to 2.5 per cent. The difference is highly significant and is probably a result of the continuation of anticoagulant therapy.

Results from study of both series of cases clearly indicate that early ambulation is not accompanied by an increased risk to the patient with myocardial infarction.

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Correlation of degree of pulmonary hypertension with morphology of the QRS in Lead V_1 in cases with evidence of systolic overloading of the right ventricle

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In recent years, attempts have been made to correlate the morphology of the tracings obtained with the right precordial electrocardiographic leads with the right ventricular pressure.[1-10] In most of these studies the two types of right ventricular overloading were not separated.[11,12,16] The present analysis was undertaken to study the correlation between the initial component of the QRS complex in Lead V_1 and the ratio of right ventricular to systemic systolic pressure in cases of systolic overloading of the right ventricle.

Material and method

The material was selected from 1,070 consecutive catheterizations of the right heart. In 227 cases there was hemodynamic and anatomic evidence of impedance to right ventricular emptying, which resulted in systolic overloading of the right ventricle. We considered right ventricular hypertension to be present if right ventricular pressure was above 40 mm. Hg; however, in an attempt to exclude cases of flow hypertension, we did not include cases of ventricular septal defect and atrial septal defect unless right ventricular pressure was above 50 mm. Hg.

These cases were classified according to the ratio of the right ventricular to systemic systolic pressure: Group I—right ventricular pressure greater than systemic pressure by 15 mm. Hg or more; Group II—right ventricular pressure and systemic pressure balanced, showing a pressure difference of no more than 15 mm. Hg; Group III—systemic pressure greater than right ventricular pressure by 15 mm. Hg or more.

Most pressures were recorded simultaneously in the right ventricle and a systemic artery, but in a few cases the left ventricular pressures were recorded. It is recognized that pressures in the femoral or radial artery may be higher than pressure in the left ventricle, and this was noted, at times, in this series.[28] Consequently, a spread of 15 mm. Hg was used to separate these groups.

Electrocardiograms were recorded in the standard fashion, and Lead V_1 was selected for analysis. This lead was chosen since it is universally used. It can be accurately placed by easily recognized anatomic landmarks, and usually a transitional type of complex is not recorded at this position. The tracings from each of the aforementioned groups were analyzed, first, with

This work was done in the Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, Kans., under the direction of E. Grey Dimond, M.D.
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regard to the diagnosis of systolic overloading of the right ventricle, and, second, with regard to the initial component of the QRS complex in Lead V_1. The criteria followed for systolic overloading of the right ventricle are those given by Cabrera[11,12]: RS, Rs, rR, R with or without initial slurring, and qR complexes in the right precordial leads; in certain circumstances a small notched QRS complex may also be found. In analyzing the initial component of the QRS complex, we used the following factors: (1) the presence of a clean R wave, (2) an initially slurred R wave, or (3) a qR complex. At times, a very small initial r, of less than 0.2 mv., followed by an R wave, was found, and this was considered to be an initial slurring of the R wave. Vectorcardiograms were taken in most of the cases, using the Grishman cube reference frame.

Results

Group I. In 28 cases the right ventricular pressure was greater than the systemic pressure; in 22 cases (78 per cent) there was a q wave in Lead V_1; and in 6 cases (22 per cent) there was initial slurring of the upstroke of the R wave in Lead V_1.

The anatomic diagnoses were: atrial septal defect with pulmonary stenosis, 13 cases; pulmonary stenosis with intact septum, 10 cases; mitral stenosis, 2 cases; atrial septal defect with pulmonary hypertension, 2 cases; primary pulmonary hypertension, 1 case.

Group II. In 114 cases there were balanced right ventricular and systemic pressures; in 87 cases (77 per cent), initial slurring of the upstroke of the R wave in Lead V_1; in 16 cases (14 per cent), a clean R wave in Lead V_1; in 6 cases (5 per cent), no electrocardiographic evidence fulfilling the criteria for systolic overloading of the right ventricle.

The anatomic diagnoses were: tetralogy of Fallot, 43 cases; ventricular septal defect with pulmonary hypertension, 35 cases; transposition of the great vessels, 5 cases; ventricular septal defect with pulmonary stenosis, 5 cases; pulmonary stenosis with intact septum, 5 cases; mitral stenosis, 3 cases; atrial septal defect with pulmonary stenosis, 3 cases; pentalogy of Fallot, 2 cases; truncus arteriosus, 2 cases; atrial septal defect plus ventricular septal defect plus pulmonary hypertension, 2 cases; primary pulmonary hypertension, 2 cases; atrioventricularis communis with pulmonary hypertension, 1 case; corrected transposition, 1 case; ventricular septal defect plus patent ductus arteriosus plus pulmonary hypertension, 1 case; single ventricle, 1 case; aortic-pulmonary communication with pulmonary hypertension, 1 case.

Group III. In 85 cases, systemic pressure was greater than right ventricular pressure. In 63 cases (75 per cent) there was a clean R wave in Lead V_1; in 9 cases (10 per cent), initial slurring of the upstroke of the R wave in Lead V_1; in 13 cases (15 per cent), no electrocardiographic evidence fulfilling the criteria for systolic overloading of the right ventricle.

The anatomic diagnoses were: ventricular septal defect with pulmonary hypertension, 26 cases; mitral stenosis, 20 cases; pulmonary stenosis with intact septum, 14 cases; patent ductus arteriosus with pulmonary hypertension, 5 cases; ventricular septal defect with pulmonary stenosis, 4 cases; atrial septal defect with pulmonary hypertension, 4 cases; atrioventricularis communis with pulmonary hypertension, 4 cases; chronic cor pulmonale, 3 cases; tetralogy of Fallot after Brock operation, 1 case; aortic-pulmonary communication with pulmonary hypertension, 1 case; ventricular septal defect with pulmonary hypertension plus coarctation, 1 case; patent ductus arteriosus with pulmonary stenosis, 1 case.

Discussion

Authors frequently have stressed the poor correlation between electrocardiographic hypertrophy and anatomic hypertrophy of the heart.[13,14] More recently, closer correlation has been found when the type of work (systolic or diastolic overloading) of the heart is considered.[15,16] In our study a high percentage of electrocardiograms fulfilled

Table I

	Q wave	*Slurred R*	*Clean R*	*No systolic overloading*
Group I	78%	22%	—	—
Group II	5%	77%	14%	4%
Group III	—	10%	75%	15%

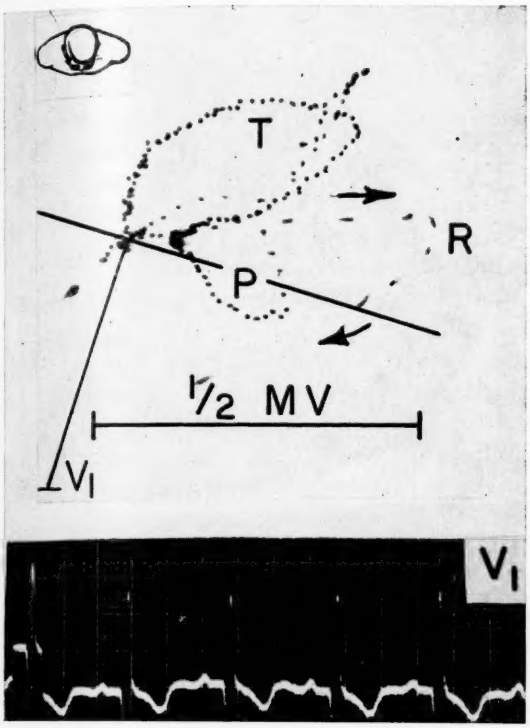

Fig. *1*. The R loop is seen pointing to the left, situated on the negative side of the Lead V_1 axis and giving a q wave on this lead. The T and P loops are also visualized (horizontal plane).

the criteria for systolic overloading of the right ventricle. At the same time, the ratio of right ventricular to systemic pressure correlated well with the configuration of the initial component of the QRS complex in Lead V_1.

Table I shows that the probability of finding a q wave in Lead V_1 in patients in whom the right ventricular pressure is greater than the systemic pressure (Group I) is 78 per cent ($p = 0.78$). In this group, conditions were found that resulted in very high right ventricular pressure, such as trilogy of Fallot and tight pulmonary stenosis, and no case of an open ventricular septum was found. These findings suggest that a ventricular septal defect, with or without another defect, is an unlikely diagnosis in the presence of a q wave in Lead V_1. The explanation of this q wave is controversial. On the basis of animal experimentation, Sodi-Pallares states that the right atrium is enlarged and that this dilated chamber transmits its variation in potential to the right precordial leads.[17,18] It is known that in the absence of myocardial infarction or complete right bundle branch block, a qR complex is usually found in cases of severe systolic overloading of the right ventricle, so that the presence of an enlarged right atrium is almost obligatory in these cases.[3] Myers showed that in cases of right ventricular hypertrophy, qR or QR patterns were recorded in leads near the right atrioventricular groove, suggesting right-to-left septal activation.[19,21] This correlates well with the known anatomic finding which shows the right ventricular portion of the interventricular septum to be the predominant septal muscular mass in cases of severe right ventricular hypertrophy.[17,20] The horizontal loop of the vectorcardiogram in the cases of our Group I revealed the initial component to be deviated posteriorly and to the left, even with high amplification, suggesting that the predominant septal vectors are from right to left[20,21] (Fig. 1). If this is true, we can infer that the septal activation is directly related to the thickness of the respective left or right portions of the septum.

There is a probability of 77 per cent ($p = 0.77$) of finding initial slurring of the upstroke of the R wave in Lead V_1 when

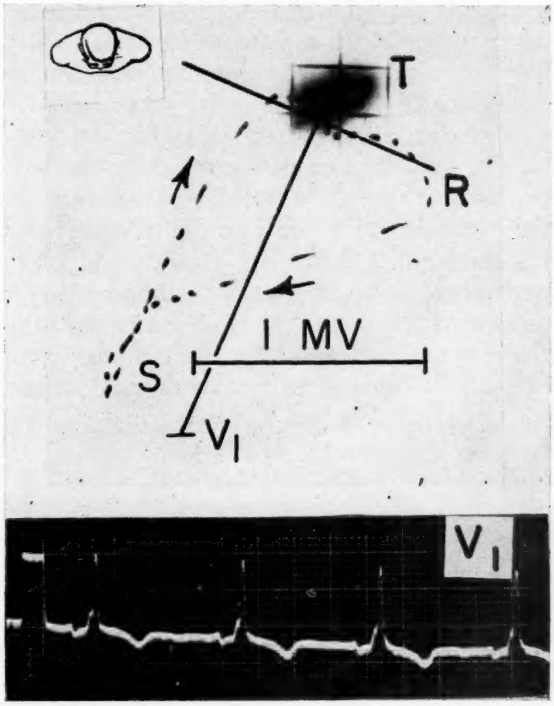

Fig. *2*. The initial component of the QRS loop is perpendicular to the Lead V_1 axis, giving an initial slurring of QRS in Lead V_1 (horizontal plane).

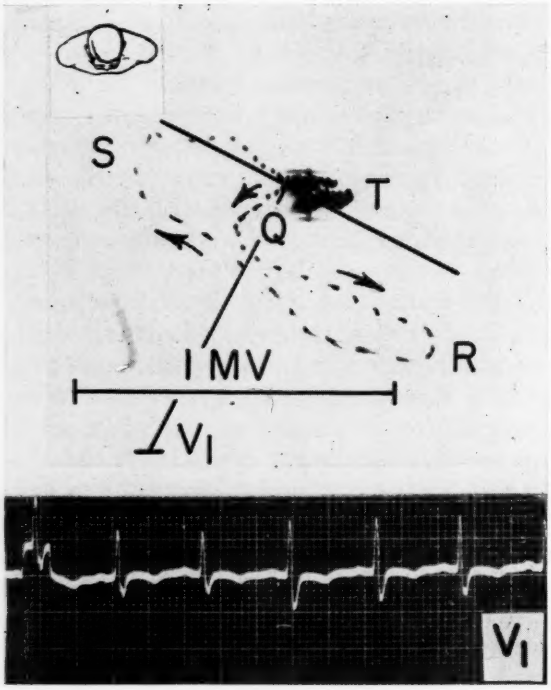

Fig. 3. Almost all of the QRS loop is on the positive side of Lead V_1. Note the clean R wave (horizontal plane).

the right ventricular pressure is balanced with the systemic pressure (see Table I and Fig. 2). We found in Group II a high incidence of conditions with open ventricular septum. We know according to hemodynamically well-established facts that in ventricular septal defect the right ventricular pressure cannot be higher than the left ventricular pressure unless the defect is very small.[27] Tetralogy of Fallot and ventricular septal defect with pulmonary hypertension were the most common abnormalities in this group, and transposition, truncus arteriosus, and pentalogy occurred only in this group. In Group II, only 5 per cent of the cases had a q wave in Lead V_1 (see Table I); so, the probability ($p = 0.05$) of finding a q wave in Lead V_1 when the pressures in the ventricles are balanced is very small. The initial slurring of the R wave is believed to be of septal origin.[22] Sodi-Pallares has recorded intracavitary electrocardiograms on the surface of the right septum in cases with initial slurring of the R wave in the right precordial leads. He found some delay in the arrival of the activation wave at the lower portions of the right septum. Because the delay correlated very well with the initial slurring of the R wave in Lead V_1, and because he considered this delay to be an indication of some degree of right bundle branch block, he concluded that the initial slurring meant a partial block.[24] Velasco and associates[23] suggest that large right septal vectors in systolic overloading of the right ventricle neutralize the left septal vectors.

In Group III, 75 per cent of the cases showed a clean R wave in Lead V_1. Since in this group the right ventricular pressure was below the left ventricular pressure or systemic pressure, there was a 75 per cent probability ($p = 0.75$) that cases with this pressure ratio would have a clean R wave in Lead V_1. The conditions more frequently found in this group were ventricular septal defect with pulmonary hypertension, mitral stenosis, and pulmonary stenosis with intact septum. In 10 per cent of the electrocardiograms in this group ($p = 0.10$), we found an initial slurring of the R wave in Lead V_1. In most of these cases the right ventricular pressure was near (within 15 mm. Hg) the level of systemic or left ventricular pressure. An RS pattern in Lead V_1 was found very frequently in this group. The clean R wave of the cases of Group III could be explained by the sum of the left septal vectors and right free ventricular wall vectors (Fig. 3). Furthermore, we believe that the ratio of right ventricular to systemic pressure is directly responsible for the septal conditions that give rise to this type of QRS-complex alteration. In 15 per cent ($p = 0.15$) of the cases in Group III, we found no evidence of systolic overloading of the right ventricle, and most of these tracings showed diastolic overloading of the right ventricle. These were, most frequently, cases of ventricular septal defect and atrial septal defect with moderate elevation of right ventricular pressure. A qR pattern was not found in Group III. In our few cases of chronic cor pulmonale a pattern compatible with systolic overloading of the right ventricle was not found, probably because the heart is often anatomically displaced inferiorly by pulmonary emphysema.[25]

We believe that a specific electrocardiographic pattern which can be correlated with proved hemodynamic findings has considerable practical diagnostic significance.

The electrocardiogram does not invariably reflect the hemodynamic changes in the heart, possibly because of the sensitivity of the lead system to influences such as body shape and the electrical position of the heart. It is hoped that the new corrected orthogonal lead systems will better reflect the hemodynamic conditions.

Summary and conclusions

1. A study of the initial component of the QRS complex in Lead V_1 and its relationship to the right ventricular–systemic pressure ratio in cases of systolic overloading of the right ventricle is presented. Three groups were studied and classified according to the right ventricular–systemic pressure ratio.

2. In the group in which the right ventricular pressure was greater than the left ventricular pressure, 78 per cent of the tracings had a qR complex; in the group in which there were balanced pressures in the ventricles, 77 per cent had an initial slurring of the upstroke of the R wave, and in the group in which the left ventricular pressure was greater than the right ventricular pressure, 75 per cent of the tracings had a clean R wave.

3. These electrocardiographic findings are shown to be useful in the differentiation of conditions with open or closed ventricular septum.

4. An explanation of the behavior of the initial component of the R wave in Lead V_1 is attempted, with emphasis on the importance of right ventricular hypertrophy.

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Right bundle branch system block in healthy young people

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Instances of right bundle branch system block* (RBBSB) pattern for which no underlying cause is clinically apparent are found sporadically among young individuals and in electrocardiographic surveys of apparently healthy populations.[1-10] The significance of the electrocardiographic pattern in any particular case is usually a matter of speculation. The block pattern in such cases could reasonably be regarded as: (1) a normal variant, (2) an indication of increased diastolic (input) load of the right ventricle, as in uncomplicated interatrial septal defect, or (3) an "isolated" abnormality of intraventricular conduction. Results of right heart catheterization in such cases have rarely been reported.[7]

This communication deals with the clinical and hemodynamic findings in 4 such individuals. The significance of the apparently isolated electrocardiographic abnormality is assessed.

Method

Each of the 4 cases was drawn from the files of the Cardiac Catheterization Unit on the basis of a clear-cut electrocardiographic pattern of RBBSB for which no underlying cause was clinically apparent. Complete right bundle branch system block was considered to be present when the QRS duration in any limb lead was 0.11 second, or greater, in association with a broad prominent secondary R wave (R′) in the right precordial leads. Incomplete right bundle branch system block was diagnosed when the contour was as described above but the QRS duration in any limb lead did not exceed 0.10 second. Right heart catheterization was performed as described previously.[11] In addition, the right ventricular electrical-mechanical (E-M) interval was determined in each case. This is the interval between the onset of QRS in the electrocardiogram (Lead II) and the simultaneously recorded rise in right ventricular systolic pressure. Measurement was made to the nearest 0.01 second, and 0.005 second was then subtracted in order to correct for the mechanical delay in transmission of the pulse through the catheter.[7] Normal criteria for the E-M interval were established on the basis of this measurement in 15 cases in which electrocardiographic and hemodynamic findings were normal.

Results

Clinical data, pertinent to the heart, are summarized in Table I. The electrocardiograms are shown in Figs. 1 and 2. The right bundle branch system block pattern

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*The term *right bundle branch system block* is used in recognition of the uncertainty in distinguishing a defect of conduction in the main bundle branch from a conduction defect in the free wall.[46]

Table I. *Summary of clinical data*

Case number	*Sex*	*Age (yr.)*	*Symptoms*	*Auscultation*	*Radiologic findings*	*Remarks*
1.	M	15	None	P_2* widely split, fixed; M_1† soft, widely split; Grade 2‡ mid-systolic murmur in second left intercostal space	Normal	Murmur since birth; interatrial septal defect suspected
2.	F	17	None	P_2 widely split, fixed; M_1 widely split; Grade 2 mid-systolic murmur in fourth left intercostal space	Normal	——
3.	F	30	Questionable dyspnea during pregnancy only	P_2 widely split, fixed; Grade 2 mid-systolic murmur in second left intercostal space	Slight dilatation of ascending aorta; "forceful" hilar pulsations	Atrial septal defect suspected
4.	M	17	Questionable dyspnea during exercise at capacity	Normal	Slight transverse enlargement of heart in posteroanterior projection	Pectus excavatum; trained athlete

*Second sound at the pulmonary area.
†First sound at the mitral area.
‡Out of Grades 1-6.

was complete in the first 3 cases, and incomplete in the fourth. QRS durations and E-M intervals are listed in Table II along with control data. It can be seen that the E-M interval is definitely prolonged in each case. The usual catheterization data were within normal limits at rest in all instances, according to previously delineated criteria.[11] In Cases 2 and 3 the hemodynamic responses to mild exercise were normal, and in Case 4 the hemodynamic response to exercise at capacity was normal. There has been a 3-year follow-up of the first 3 cases, during which time no change in clinical or electrocardiographic status was noted.

Discussion

In a recent study of 100 healthy subjects, Bryant[9] found secondary R waves in certain right precordial leads in 95 per cent of the subjects who were under 40 years of age and in 22 per cent of the subjects who were beyond 40 years of age. It was postulated that these patterns reflect a *normal* order of ventricular activation and represent projection on appropriate leads of electrical potentials from the region of the outflow tract of the right ventricle, usually the last part of the myocardium to be activated.[12,13] However, in the 4 cases of this report the electrocardiographic alterations were found to be more marked than those described by Bryant and co-workers[9,14,15] and others.[16] Furthermore, prolongation of the interval between onset of electrical systole and onset of right ventricular mechanical systole, a constant feature in this series (Table II), provides evidence that the electrocardiographic contour in these cases cannot be regarded as a normal variant. A significant prolongation of this interval, when compared with the normal, would appear to be a valid indication of abnormal delay in onset of right ventricular contraction, and, thus, of slowed right intraventricular conduction. An incomplete RBBSB pattern, such as that in Case 4 of this series, has been reported in other instances of pectus excavatum and attributed to an unusual rotation of the heart.[17] Again, such an

explanation does not satisfy the present case in view of the prolonged E-M interval.

Diastolic (input) overload of the right ventricle, as typified by interatrial septal defect, is commonly associated with an RBBSB pattern,[18,19] usually incomplete. Recent studies suggest that this pattern may not be due to actual delay in right intraventricular conduction, but rather to right ventricular outflow tract *hypertrophy* which exaggerates the terminal QRS forces, with or without alteration in position of the heart related to enlargement on the right side[20,21]; in such cases the right ventricular E-M interval is usually, but not invariably, normal.[7,20,22,23] On the other hand, a RBBSB pattern does not necessarily imply the presence of right ventricular hypertrophy, and the latter is notoriously difficult to recognize from the electrocardiogram in the presence of unequivocal RBBSB.[9,24] In the present group of cases any component of hypertrophy seems to be ruled out on the basis of right heart catheterization, which failed to reveal the presence of intracardiac shunts or of abnormal levels of pressure. It has been stated that the electrocardiographic pattern associated with right ventricular diastolic overload may be distinguished from a conduction delay in the right bundle branch (with prolonged E-M interval) vectorcardiographically,[7] or by simultaneous recording of certain scalar leads (see Schultz in Reference 25). However, the former has been disputed,[26] and a RBBSB pattern associated with prolongation of the E-M interval is sometimes found in proved cases of interatrial septal defect.[7,22,23]

Table II. *Relationship of* QRS *duration to electrical-mechanical* (E-M) *interval*

Case number	*QRS duration* (*sec.*)	*E-M interval* (*sec.*)
1.	0.14	0.105
2.	0.14	0.135
3.	0.12	0.095
4.	0.09	0.095
Controls (15 cases)	Range 0.06–0.08	Range 0.055–0.075

This study is in keeping with a previous one of Braunwald and associates[7] in demonstrating that the fully developed pattern of RBBSB in young people without evidence of associated heart disease indeed reflects a defect in intraventricular conduction. However, it sheds no light directly on the etiology or pathogenesis of the conduction disturbance. It is not known whether the conduction disturbance dates from birth, nor is it known whether there is actual anatomic involvement of the right bundle branch. Recent suitably detailed correlative studies of *seriously diseased* hearts indicate that complete RBBSB is almost always associated with an organic lesion of the right bundle branch,[27,28] whereas incomplete RBBSB is commonly associated with right ventricular hypertrophy, and in only about one quarter of the cases with definite involvement of the right bundle branch.[27]

Because this electrocardiographic pattern is associated with interruption of the right bundle branch experimentally, and with known heart disease clinically, the tendency has been to assume that an organic lesion is in all probability at the root of all such disturbances in conduction.[29,30] Moreover, it has been suggested that, because of the very nature of its morphology,[31] the right bundle branch is more likely to be affected by localized, otherwise benign, organic processes than is the left bundle branch,[30] and "isolated" left bundle branch system block in young individuals is indeed relatively rare.[4,6,32] However, on the assumption that the conduction defect reflects organic involvement of the right bundle branch, consideration of reasonable etiological possibilities does not bring to mind any single one likely to satisfy the present and similar cases. The conduction defect in such cases has been attributed, for example, to a *congenital* deformity of the right bundle branch system,[1,3] but such actual deformity has been described only rarely, and then in association with severe heart disease.[27,33] Although *arteriosclerotic coronary artery disease* is certainly a most common cause of RBBSB, and pathologic evidence of coronary artery involvement has been found not infrequently in relatively young males, it appears unlikely that it could be consistently the basis of

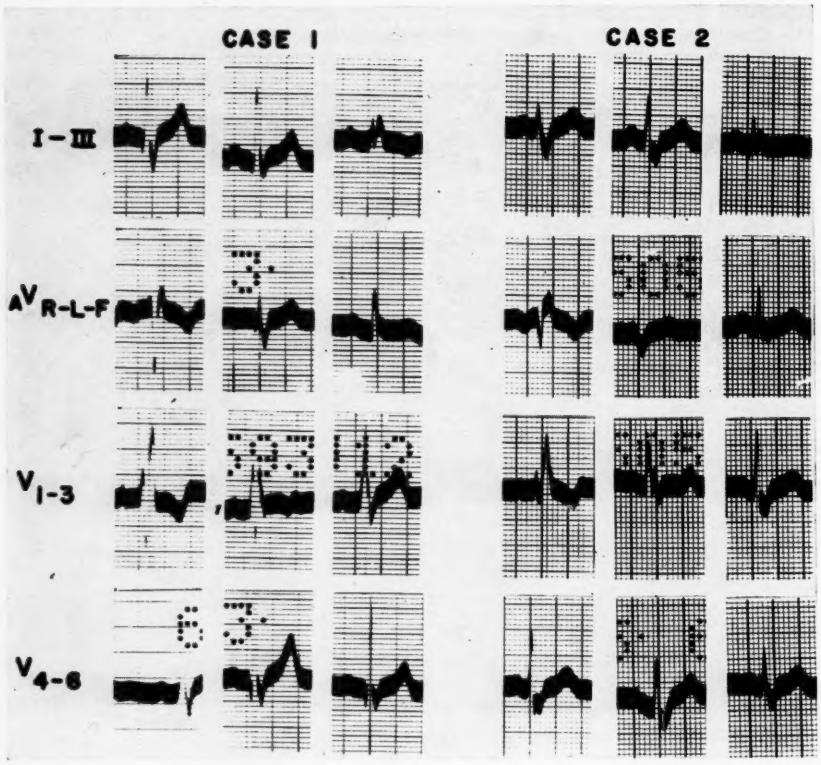

Fig. *1.* Electrocardiograms of Cases 1 and 2. See text.

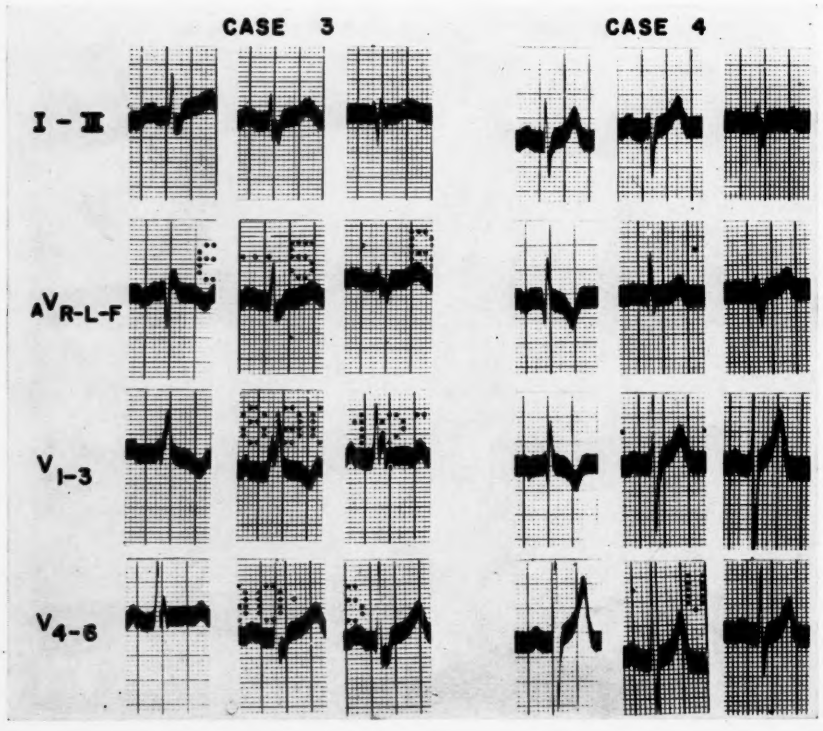

Fig. *2.* Electrocardiograms of Cases 3 and 4. See text.

the electrocardiographic findings in this group (in which 2 of the subjects were females and 3 were under 18 years of age). Such defects in conduction have been attributed to an otherwise benign or clinically inapparent *myocarditis*.[5] This hypothesis is attractive. The clinical incidence of myocarditis is observed to be less than the pathologic,[34] for the diagnosis is easily missed in life. However, RBBSB is a rather uncommon feature of known myocarditis,[34,35] and when present in instances of "nonspecific" (viral) myocarditis it usually appears to be associated with the clinically and pathologically more severe or chronic cases,[36] or to be accompanied, on late follow-up, by other stigmata of heart disease.[37] Cases of known myocarditis manifested at some stage by RBBSB alone might link this etiology with the present cases, but except for certain instances of chronic Chagas' disease,[38] no such documentation could be found. There was no history of acute rheumatic fever in the present cases, and in none were there characteristic murmurs that might implicate *rheumatic heart disease*.

Although the conduction defect in these cases could perhaps have a basis of multiple etiologies, the difficulty of establishing any particular one raises the question: Need there be an organic basis? It should be stressed that the finding of an electrocardiographic pattern of right bundle branch block similar to that produced experimentally does not prove the presence of a corresponding bundle branch lesion in man. Actually, the electrocardiogram does not differentiate among three possibilities: (1) complete (anatomic) interruption of conduction in a main bundle branch, (2) anatomic interruption of conduction in a parietal portion of the conduction system, and (3) mere *slowing* of conduction in some part of a main bundle branch so that activation of the right ventricle is effected via transseptal impulse conduction from the left.[28] Simple prolongation of the relative refractory period somewhere along the conduction system, in relation to the usual heart rate, could have such an effect, and instances of intermittent, at times rate-dependent, RBBSB are not uncommon in young healthy individuals as well as in older individuals with or without associated heart disease.[3,6,9,39,40] With particular regard to the last of these three possible mechanisms, the line between involvement by disease and physiologic variation becomes thin indeed, and it remains to be proved that the disturbance in conduction, although giving rise to an abnormal electrocardiogram, is in any way the result of a disease process. It has been suggested in the past that RBBSB may at times be "physiologic,"[41] or, in cases such as the present ones, may have a "physicochemical" rather than an organic basis.[4]

As long ago as 1925,[42] it was recognized that an electrocardiographic pattern of RBBSB does not of itself imply a poor prognosis. Subsequent studies,[1-5,43] including cases followed up for almost 30 years, have tended to fortify this point of view, and it is now accepted that the prognosis of a patient with a RBBSB pattern is determined by the underlying heart disease.[29,44,45] Thus, it appears unjustified at present to attach the stigma of heart disease, however benign, to cases such as those in the present study, in which RBBSB is present but is unassociated with clinical or laboratory evidence of cardiac pathology.

Summary

The electrocardiographic pattern of right bundle branch system block was an isolated finding in a group of 4 young individuals who were apparently normal on the basis of clinical and hemodynamic evaluation. Prolongation of the right ventricular electrical-mechanical interval provided evidence that the electrocardiographic abnormality was attributable to a conduction defect in the right side rather than to right ventricular hypertrophy or to a physiologic variant of contour. The significance of the electrocardiographic abnormality in such cases is discussed. It is concluded that the finding of an "isolated" right bundle branch system block in a young and apparently healthy individual cannot, of itself, be taken to indicate prima facie evidence of organic heart disease.

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Experimental and laboratory reports

The production of lactic acid during exercise in normal subjects and in patients with rheumatic heart disease

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It has been shown that the concentration of lactic acid in the blood (capillary, arterial, or superficial venous) of patients with heart disease is greater than that in normal subjects during a similar degree of exercise.[1-5] Weiss and Ellis[6] also demonstrated that the oxygen content was lower and the concentration of lactic acid higher in the femoral venous blood of patients with heart disease than in that of normal subjects immediately after similar leg exercise. Many patients with heart disease are unable to increase the cardiac output to a normal degree during exercise.[7] Despite a remarkable reduction of blood flow through certain regional circulations (splanchnic, renal, nonexercising muscle and skin[8]), the blood flow through the exercising limbs is less than that in normal subjects under the same conditions.[9] Since almost all of the increased oxygen uptake is in the exercising muscles, the oxygen content of the blood returning from the exercising limbs is considerably less than that in normal subjects during similar exercise.[9] Therefore, the oxygen tensions in the exercising muscles must be lower than those in normal subjects. It has been assumed that the increased production of lactic acid in such patients during exercise is due to the influence of lowered oxygen tensions on the metabolism of exercising muscle. The reduction of blood flow through the liver and kidney may, however, also delay the catabolism and excretion of lactic acid during exercise. Furthermore, the marked reduction of blood flow through many other tissues not involved in the exercise may reduce the amount of lactic acid diffusing into or even being catabolized by these tissues.

The purpose of the present study has been to investigate more precisely the relationship between the hemodynamic response to exercise and the production of lactic acid in normal subjects and in patients with heart disease of varying severity. Direct measurements of the concentration of lactic acid and oxygen in the arterial blood and venous blood leaving the exercising legs have been carried out in an attempt to discover a more precise relationship between the rate of production of lactic acid in exercising muscle, the

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Table I. *Details concerning normal subjects and patients studied*

Subject number	*Sex*	*Age (yr.)*	*Weight (Kg.)*	*BSA ($M.^2$)*	*Diagnosis*
			Group A		
A807	F	50	68.2	1.72	Normal
A822	F	36	55.5	1.54	Normal
A832	F	37	59.1	1.57	Normal
A812	F	59	58.6	1.58	"Primary" pulmonary hypertension
A824	F	36	55.9	1.55	Mitral stenosis. Aortic stenosis and incompetence (F)
A828	F	28	56.4	1.60	Mitral stenosis and incompetence (F)
A834	F	39	80.5	2.05	Mitral stenosis and incompetence (F)
A836	F	46	62.7	1.64	Mitral stenosis (F)
A840	M	42	50.9	1.61	Mitral stenosis (F)
A842	F	35	59.1	1.59	Mitral stenosis
A850	F	38	54.1	1.50	Mitral stenosis (F)
A854	F	50	52.3	1.53	Mitral stenosis and incompetence. Aortic stenosis (F)
A857	F	18	52.7	1.54	Mitral stenosis and aortic incompetence
A865	F	37	56.4	1.56	Mitral stenosis
A875	M	45	61.8	1.68	Mitral stenosis (F)
			Group B		
A774	F	24	61.4	1.62	Normal
A780	F	25	39.1	1.35	Mitral stenosis
A785	F	33	41.8	1.32	Mitral stenosis
A787	F	54	51.8	1.54	Mitral stenosis. Systemic hypertension (F)
A791	M	37	50.0	1.57	Mitral stenosis. Aortic incompetence. Tricuspid stenosis (F)
			Group C		
A810	M	46	60.9	1.71	Normal
A833	M	44	52.7	1.60	Normal
			Group D		
A920	F	41	52.3	1.62	Normal
A795	F	36	40.9	1.32	Mitral stenosis and aortic incompetence (F)
A801	F	42	68.2	1.74	Mitral stenosis and incompetence (F)
A803	M	45	73.2	1.91	Mitral stenosis (F)
A821	M	38	74.5	1.91	Mitral stenosis and aortic incompetence (F)
A917	F	55	62.7	1.71	Myocarditis
A927	F	45	66.8	1.84	Mitral stenosis (F)
A929	F	35	44.5	1.39	Mitral stenosis. Aortic stenosis and incompetence
A934	F	28	50.9	1.49	Mitral stenosis and aortic incompetence

(F): Auricular fibrillation.

oxygen uptake, and the levels of oxygenation of the blood returning from the exercising leg. The validity of the assumption that the concentration of lactic acid in blood collected from the nonexercising areas is proportional to the rate of production of lactic acid in the exercising muscles during a relatively steady state has also been investigated.

The concentration of lactic acid in arterial blood during rest was also measured in 41 patients confined to bed. Seventeen of these patients had normal hearts and lungs, and the other 24 had severe

Table II. *The effect of exercise on the levels of lactic acid in the arterial and femoral venous blood of Groups A, B, and C*

Subject number	*Group*	*BA or FV*	*Lactic acid (mg./100 ml. of blood)*							*Fem. VA_L / Fem. AV_{O_2} (exercise) (mg. lactic acid/ml. O_2)*	*R_{O_2} (exercise)*	*$\dot{M}_L$ (exercise) (mg./min.)*
			Rest		*Exercise*				*Recovery*			
					6 min.	*8 min.*	*10 min.*	*Mean*				
					Normal Subjects							
A807	A	FV	9.6	—	11.8	12.0	11.8	11.9	14.2	+0.10	.01	17
		BA	9.2	—	10.6	11.0	12.0	11.2	12.2			
A822	A	FV	15.0	15.2	33.0	32.4	31.4	32.2	18.6			
		BA	13.2	12.8	27.8	27.4	27.4	27.5	16.4	+0.41	.05	244
A832	A	FV	9.7	10.0	37.2	43.2	39.4	40.0	21.8			
		BA	10.1	10.4	32.8	38.0	38.0	36.3	20.0	+0.34	.04	260
A774	B	FV	13.8	—	30.6	30.2	31.4	30.8	—			
		BA	11.8	—	23.6	26.0	27.4	25.7	—	+0.49	.06	290
A774	B	FV	7.0	—	46.8	46.8	45.8	46.5	—			
		BA	6.8	—	36.8	38.4	40.0	38.4	—	+0.70	.09	625
A810	C	FV	9.2	—	13.4	13.0	12.2	12.9	10.6			
		BA	8.6	—	12.8	12.2	11.2	12.1	9.6	+0.07	.01	32
A833	C	FV	9.2	9.6	75.6	70.8	70.8	72.4	35.0			
		BA	8.0	9.2	61.8	68.4	66.0	65.4	28.6	+0.42	.05	453

VA_L = Venoarterial difference of lactic-acid concentration (mg./100 ml.).
AV_{O_2} = Arteriovenous difference of oxygen content (ml./100 ml.).

$$R_{O_2} = \frac{\text{Venoarterial difference of lactic acid (mM./L.)} \times 0.5}{\text{Arteriovenous difference of oxygen (mM./L.)}}$$

BA = Brachial arterial blood. FV = Femoral venous blood.
$\dot{M}_L$ = Estimated blood flow in leg during exercise (L./min.) × VA_L (mg./100 ml.) × 10 = rate of liberation of lactic acid into femoral blood (mg./min.).

heart disease. Thirteen of these patients with heart disease had shortness of breath on slight or moderate exertion (Grade III according to the New York Heart Association classification), and the other 11 were in frank clinical congestive heart failure as evidenced by an abnormally raised systemic venous pressure with or without edema (Grade IV).

Methods

The estimation of lactic acid in blood has been carried out on 5-ml. samples, using the method of Barker and Summerson[10] as modified by Mitchell and Cournand[11]; the blood was hemolyzed in water immediately after collection. In this laboratory, the mean and standard deviation of the difference of 43 pairs of blood samples taken 2 minutes apart from the same blood vessel during rest were 0.38 and 0.315 mg./100 ml., respectively; the average of all readings was 10.28 mg./100 ml.

Preliminary studies of the effect of exercise in normal subjects and in patients with heart disease showed that the concentration of lactic acid in arterial blood rose rapidly during the first few minutes and then achieved a steady level by about the fifth minute. It was found that, if exercise was continued beyond this time, however, the concentration of lactic acid usually diminished again after about the tenth to fifteenth minute of exercise, although the rate of external work and the oxygen uptake remained unchanged. This phenomenon was originally described in normal subjects by Bang.[12] Since the length of exercise that can be undertaken by patients with heart disease is limited, a period of 10 minutes of exercise was chosen, and the levels of lactic acid in the brachial

arterial and femoral venous blood were measured during the second half of this period. It was hoped that, at this time, a reasonably steady level of lactic acid in the blood would be maintained between the initial rise and subsequent decline, and evidence will be presented that this was so.

The effects of exercise were studied in 7 healthy subjects and in 24 patients with heart disease. Details of the normal subjects and of the patients are given in Table I. It will be noted that all except 2 of the patients had rheumatic heart disease. Of the two exceptions, one had pulmonary hypertension of unknown etiology, and the other had developed recurrent heart failure without any demonstrable valvular or congenital heart disease, pulmonary or systemic hypertension, or evidence of coronary disease. There was no evidence of peripheral vascular disease or

Table II. *The effect of exercise on the levels of lactic acid in the arterial and femoral venous blood of Groups A, B, and C—Cont'd*

Subject number	*Group*	*BA or FV*	*Lactic acid (mg./100 ml. of blood)*							*Fem. VA_L* / *Fem. AVo_2 (exercise) (mg. lactic acid/ml. O_2)*	*Ro_2 (exercise)*	*$\dot{M}_L$ (exercise) (mg./min.)*
			Rest		*Exercise*				*Recovery*			
					6 min.	*8 min.*	*10 min.*	*Mean*				
						Cardiac Patients						
A812	A	FV	11.8	—	36.0	32.4	32.0	33.5	15.0			
		BA	10.4	—	28.8	28.2	28.2	28.4	13.0	+0.28	.03	81
A824	A	FV	8.7	8.8	23.4	23.2	22.6	23.1	12.9			
		BA	7.2	7.6	17.8	17.9	18.2	18.0	9.8	+0.41	.05	94
A828	A	FV	8.3	9.2	39.2	37.2	36.0	37.5	20.1			
		BA	7.7	8.4	34.4	32.2	32.4	33.0	16.4	+0.40	.05	244
A834	A	FV	11.5	11.9	14.4	14.4	15.0	14.6	15.4			
		BA	10.0	10.1	13.1	13.2	13.4	13.2	12.7	+0.08	.01	16
A836	A	FV	11.4	10.8	105.8	116.4	111.6	111.3	71.4			
		BA	9.6	—	92.4	97.2	94.8	94.8	67.2	+0.82	.10	615
A840	A	FV	10.4	10.5	30.8	32.5	33.2	32.2	10.8			
		BA	9.2	8.4	25.6	25.9	26.1	25.9	13.6	+0.38	.05	180
A842	A	FV	10.2	10.0	33.7	34.4	33.2	33.8	16.7			
		BA	9.3	10.4	28.8	30.2	30.1	29.7	13.6	+0.34	.04	264
A850	A	FV	14.0	14.0	37.0	40.8	46.0	41.2	20.5			
		BA	11.9	12.1	25.6	31.8	34.2	30.5	15.3	+0.62	.08	100
A854	A	FV	8.8	8.6	32.0	29.8	28.6	30.2	12.5			
		BA	7.2	7.3	24.8	25.4	24.4	24.9	—	+0.33	.04	158
A857	A	FV	9.1	9.1	69.4	80.0	80.4	76.6	38.8			
		BA	8.4	7.8	66.8	65.8	66.2	66.3	33.5	+0.74	.09	716
A865	A	FV	9.4	9.3	50.8	51.4	46.2	49.4	22.8			
		BA	7.8	8.0	41.0	43.0	41.8	41.9	18.9	+0.57	.07	420
A875	A	FV	10.4	10.6	97.8	103.8	107.4	103.0	70.4			
		BA	8.5	8.7	85.5	96.9	95.7	92.7	70.4	+0.51	.06	852
A780	B	FV	11.2	—	42.4	44.0	44.2	43.5	21.6			
		BA	9.8	—	27.6	29.2	32.0	29.6	16.6	+0.88	.11	117
A785	B	FV	13.0	3.0	31.6	29.2	28.0	29.6	15.0			
		BA	12.0	11.8	28.0	27.2	24.4	26.5	—	+0.26	.03	93
A787	B	FV	18.8	19.2	24.0	23.8	25.2	24.4	17.4			
		BA	20.0	20.4	23.0	23.8	25.4	24.1	20.0	+0.03	<.01	5
A791	B	FV	12.0	12.6	40.0	47.2	49.6	45.6	25.0			
		BA	10.8	10.0	34.0	40.2	46.8	40.3	22.0	+0.43	.05	185

For footnotes, see first section of Table II on opposite page.

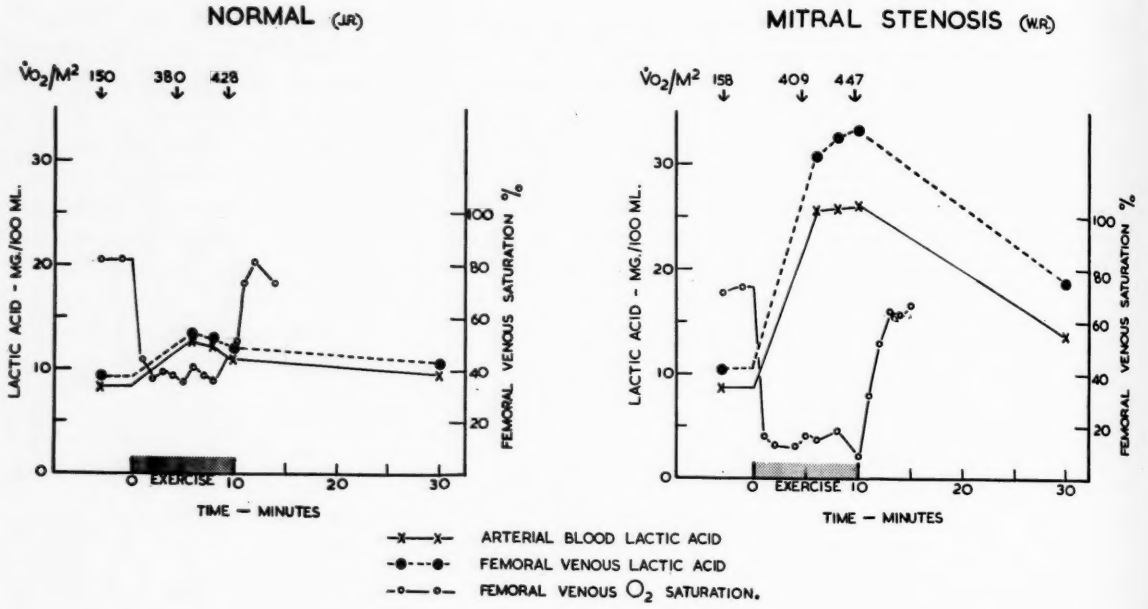

Fig. *1.* The effect of leg exercise on the concentration of lactic acid in arterial and femoral venous blood and on the femoral venous blood oxygen saturation in a normal subject and in a patient with mitral stenosis at similar levels of exercise.

embolization in any of the patients studied, either in the history or on physical examination. The studies were carried out in the early afternoon. All the subjects had been confined to bed without food since breakfast and had lain on the catheterization table for at least 1 hour before exercise was begun. Sodium Amytal, 0.2 Gm., had been given 3 to 4 hours before the time of exercise. The exercise consisted of pedaling a bicycle ergometer for a period of 10 minutes in the recumbent position, the external work being maintained at a constant level. All subjects had practiced the procedure the day before so as to increase confidence and to determine the rate of work possible without undue stress.

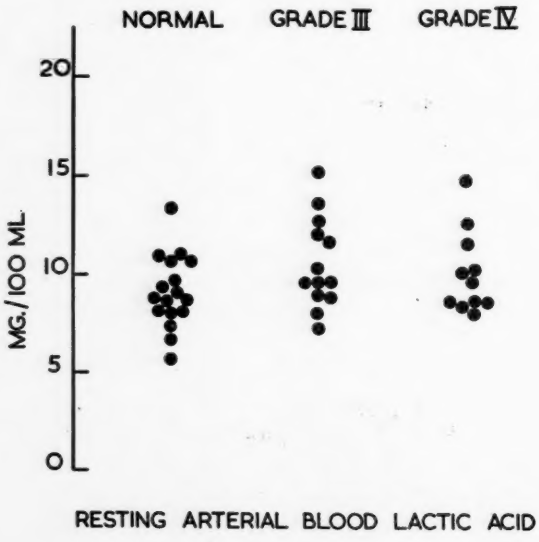

Fig. *2.* The concentration of lactic acid in the arterial blood of patients resting in bed. Three groups are compared: those with normal hearts and lungs, and those with Grade III and Grade IV cardiac disability (New York Heart Association classification).

The brachial artery was cannulated in all subjects. In 3 normal subjects and 12 patients (Group A), a cardiac catheter was placed with its tip in the pulmonary artery, and a length of polythene tubing was inserted directly through a needle into the femoral vein. While these patients exercised, samples of blood were taken every minute from the femoral vein, every other minute from the brachial artery, and from the pulmonary artery at the times of collection of expired gas. The oxygen saturation of these samples was measured by a spectrophotometric method.[13] Arterial blood oxygen capacities were measured spectrometrically at rest and at the seventh minute of exercise. Routine checks of the spectrophotometric technique against the Van Slyke method and against standardized (iron content) blood capacities were also carried out. Expired air was collected into a Tissot spirometer for a period of 3

minutes at rest, just prior to the exercise and during the fifth and tenth minutes of exercise. Samples of expired air were analyzed in a micro-Schölander apparatus. Therefore, the cardiac output at rest and at the fourth to fifth and ninth to tenth minutes of exercise could be estimated by the direct Fick method. The degree of response of the cardiac output to exercise has been graded by use of the criteria of Donald, Bishop and Wade.[14] In Grade I, the response of cardiac output to exercise is only slightly impaired; in Grade III, the cardiac output changes little or not at all in response to exercise.

In 1 normal subject studied twice and in 4 patients (Group B) the femoral vein was entered retrogradely by means of a cardiac catheter introduced into the arm. In these studies the cardiac output and its response to the same level of external work was measured 20 minutes after the initial experiment by moving the tip of the cardiac catheter to the pulmonary artery.

In 2 of the normal subjects (Group C), cardiac catheterization was not carried out, and the response of the cardiac output to exercise was assumed to be normal. In these subjects the samples of blood were drawn only from the femoral vein and brachial artery.

Group D consisted of 1 normal subject and 8 cardiac patients in whom femoral venous samples were not taken. These patients had the tip of the cardiac catheter in the pulmonary artery and a needle in the brachial artery. The period of exercise, measurement of cardiac output, and measurement of lactic acid in the arterial blood followed the same protocol as that in Groups A and B.

In all of the exercise studies the levels of lactic acid in the femoral venous and brachial arterial blood were measured at rest (usually twice), and then at the sixth, eighth, and tenth minutes of exercise. In most studies these levels were also measured 20 minutes after exercise.

Results

The concentration of lactic acid in the brachial arterial and femoral venous blood at rest, during exercise, and on recovery (20 minutes after exercise) are shown in Table II (Groups A, B, and C); and Table III details the concentration of lactic acid in the brachial arterial blood under the same conditions in Group D, in which group of subjects no samples of femoral venous blood were collected.

The oxygen uptake, ventilation, respiratory quotient, arterio-mixed venous blood

Table III. *Lactic-acid concentration in arterial blood during rest and exercise in Group D*

Case number	*Arterial blood lactic acid (mg./100 ml.)*						
	Rest		*Exercise*				*Recovery*
			6 min.	*8 min.*	*10 min.*	*Mean*	
			Normal Subject				
A920	9.4	9.3	21.8	24.6	26.5	24.3	14.3
			Cardiac Patients				
A795	8.6	—	14.2	14.8	15.2	14.7	11.4
A801	8.0	—	11.4	12.2	12.4	12.0	9.4
A803	11.4	—	58.8	60.4	61.6	60.3	26.0
A821	9.8	—	14.6	13.8	13.8	14.1	11.4
A917	12.0	11.9	48.8	58.4	55.2	54.1	29.6
A927	7.9	8.1	27.6	28.2	28.2	28.0	13.4
A929	7.4	7.2	55.5	61.1	61.2	59.3	18.0
A934	6.7	6.6	62.2	66.1	67.6	65.3	25.6

oxygen content difference, and cardiac output at rest and during exercise are shown in Table IV. The degree of response of the cardiac output to exercise[11] is also given. The high resting cardiac output of 4 of the 5 normal subjects in whom it was measured is worthy of comment. It may be recalled that similar raised values of the resting cardiac output were found in a previous study of normal healthy subjects in this laboratory.[15] These normal subjects are always medical men or women who are cognizant of the risks, slight though they may be, of the procedure. It has been shown, however, that in such subjects the exercising cardiac outputs are entirely

Table IV. *Respiratory and hemodynamic data during rest and exercise*

Case number	*Group*	*Rest*					*4-5 minutes*	
		$\dot{V}_E$	$\dot{V}_{O_2}/M.^2$	R_E	$\overline{A\,V_{O_2}}$	$\dot{Q}/M.^2$	$\dot{V}_E$	$\dot{V}_{O_2}/M.^2$
								Normal
A807	A	7.54	165	0.77	4.7	3.5	15.48	240
A822	A	4.40	134	0.71	2.5	5.3	15.57	547
A832	A	4.79	138	0.75	2.4	5.8	20.09	617
A774	B	6.98	179	0.71	3.6	4.9	20.82	557
A774	B	6.89	179	0.77	—	—	28.84	746
A810	C	9.31	150	1.02	—	—	13.69	380
A833	C	8.98	154	1.12	—	—	23.06	806
A920	D	5.01	150	0.65	3.0	5.0	13.78	463
Average		6.74	156	0.81			18.92	545
								Cardiac
A812	A	6.21	127	0.79	8.1	1.6	13.36	284
A824	A	5.68	142	0.73	5.9	2.4	9.89	273
A828	A	6.32	158	0.81	4.7	3.4	21.99	528
A834	A	7.78	108	0.71	8.2	1.3	13.20	187
A836	A	6.74	114	0.83	6.8	1.7	28.81	525
A840	A	8.27	158	0.76	6.1	2.6	17.98	409
A842	A	6.89	153	0.87	4.9	3.1	16.59	573
A850	A	6.98	167	0.81	12.9	1.3	9.68	233
A854	A	5.01	132	0.88	6.1	2.2	13.44	444
A857	A	6.36	166	0.76	3.5	4.7	32.07	758
A865	A	5.41	149	0.78	4.2	3.6	24.11	592
A875	A	7.12	147	0.74	4.9	3.0	52.25	1,191
A780	B	10.50	194	0.82	12.2	1.4	16.88	253
A785	B	5.34	142	0.85	4.1	3.5	18.4	566
A787	B	9.95	155	0.83	6.5	2.4	13.26	280
A791	B	4.52	126	0.74	6.8	1.9	16.37	383
A795	D	5.29	141	0.70	7.6	1.9	8.07	227
A801	D	5.54	147	0.82	4.6	3.2	9.23	291
A803	D	7.41	131	0.86	4.4	3.0	30.97	553
A821	D	8.81	184	0.74	8.4	2.2	15.91	282
A917	D	6.40	154	0.78	4.8	3.2	9.93	377
A927	D	4.84	128	0.72	3.6	3.5	16.22	407
A929	D	6.06	153	0.74	5.4	2.8	34.88	519
A934	D	4.27	152	0.74	3.9	3.9	14.22	633
Average		6.57	147	0.78	6.2	2.7	19.07	448

$\dot{V}_E$ = Liters of gas expired per minute (B.T.P.S.). R_E = Respiratory exchange ratio. $\dot{Q}$ = Cardiac output (L./min.). and mixed venous blood (ml./100 ml.).

comparable to those found in studies of other normal subjects who have less expert knowledge of the procedure. In the experience of this laboratory, psychological stress does not cause a hyperkinetic state during exercise. It is also to be noted that the only assumption made concerning the 2 healthy subjects whose right hearts were not catheterized was that the response of the cardiac output to exercise was normal in degree.

The mean oxygen uptake during exercise was 533 ml./min./M.^{2} (rise of 377 ml./M.^{2}) in the normal subjects, and 452 ml./min./M.^{2} (rise of 306 ml./M.^{2}) in the patients with heart disease.

of exercise			*9-10 minutes of exercise*					*$\dot{Q}$ response to exercise*
R_E	$\overline{AV}_{O_2}$	$\dot{Q}/M.^2$	$\dot{V}_E$	$\dot{V}_{O_2}/M.^2$	R_E	$\overline{AV}_{O_2}$	$\dot{Q}/M.^2$	
Subjects								
0.97	5.6	4.3	25.08	219	1.17	4.8	4.5	Normal
0.76	7.6	7.2	15.29	464	0.82	7.3	6.4	Normal
0.91	9.0	6.9	21.38	622	0.89	9.0	6.9	Normal
0.87	—	—	19.81	512	0.88	—	—	Normal
0.83	—	—	28.14	639	0.89	—	—	Normal
0.86	—	—	15.64	428	0.88	—	—	—
0.98	—	—	23.03	808	0.92	—	—	—
0.84	6.6	6.8	16.59	475	0.91	6.8	7.0	Normal
0.88			20.62	521	0.91			
Patients								
0.87	16.5	1.7	14.76	301	0.89	15.6	1.9	III
0.76	10.0	2.7	10.57	265	0.78	10.1	2.6	III
0.94	10.6	5.0	23.80	533	0.93	10.6	5.0	I
0.60	12.4	1.5	13.61	182	0.66	13.3	1.4	III
1.11	18.3	2.9	33.96	579	1.04	18.0	3.2	III
0.89	13.6	3.0	19.54	447	0.85	12.6	3.6	III
0.79	9.7	5.9	16.59	679	0.67	9.9	6.9	Normal
0.87	15.0	1.6	10.39	244	0.91	14.8	1.7	III
0.83	14.0	3.2	13.30	407	0.88	13.6	5.0	III
1.09	11.9	6.4	38.71	807	0.96	11.8	6.8	I
0.97	11.2	5.3	24.95	598	0.93	11.1	5.4	I
0.89	17.9	6.7	63.84	1,060	1.07	18.8	5.6	II
0.92	—	—	19.72	273	0.94	—	—	III
1.00	—	—	16.1	502	0.94	—	—	I
0.75	—	—	12.97	260	0.80	—	—	II
1.04	—	—	18.00	382	1.03	—	—	II
0.75	10.1	2.3	8.49	225	0.78	10.0	2.2	III
0.74	8.6	3.4	11.19	328	0.78	8.7	3.8	II
1.09	11.4	4.9	31.52	543	0.99	11.5	4.7	I
0.81	13.2	2.1	13.52	254	0.78	12.8	2.0	III
1.02	13.1	2.9	10.42	430	0.95	11.9	3.6	III
0.87	10.6	3.8	17.90	439	0.87	11.0	4.0	II
0.96	14.7	3.5	35.72	534	0.97	14.8	3.6	III
1.02	11.5	5.5	16.72	707	1.01	12.1	5.9	I
0.90			20.68	457	0.89			

$\dot{V}_{O_2}$ = Milliliters of oxygen taken up by the lungs per minute (S.T.P.D.). $\overline{AV}_{O_2}$ = Difference in oxygen content between arterial

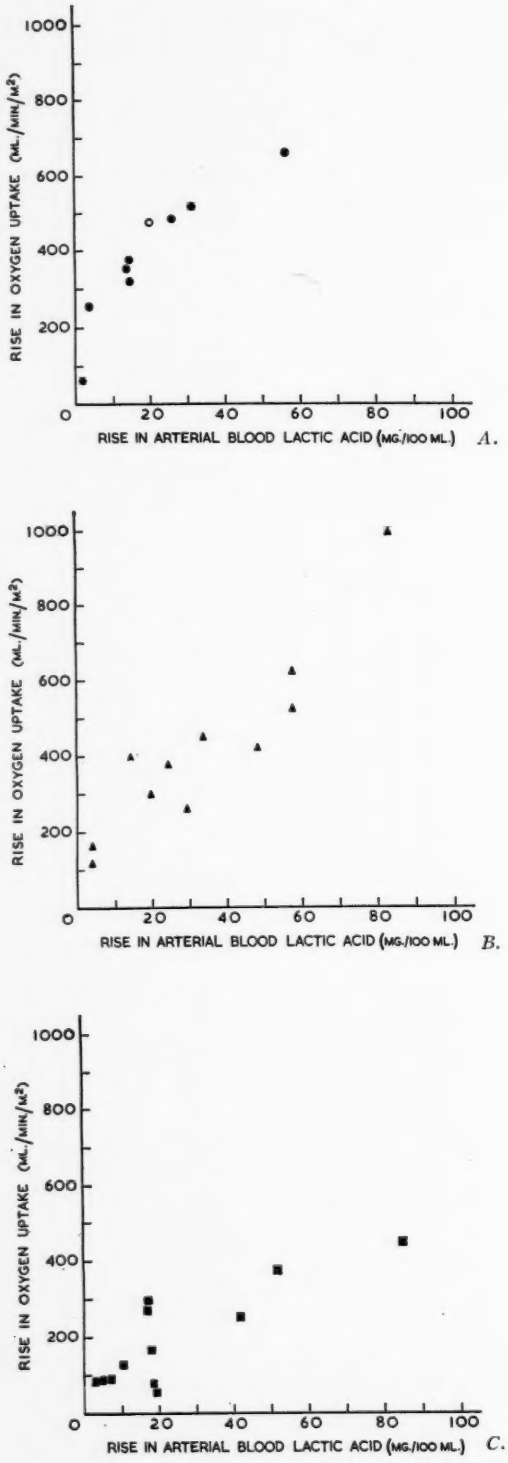

Fig. 3. The relationship of the increase in the concentration of lactic acid in arterial blood to the increase in oxygen uptake during exercise. *A:* ● = Normal subjects. ○ = Cardiac patient with normal cardiac-output response. *B:* ▲ = Patients with slight and moderate impairment of cardiac response (Grades I and II; Donald et al.[14]). *C:* ■ = Patients with severe impairment of cardiac-output response (Grade III; Donald et al.[14]).

The results of two representative exercise studies in a normal subject and in a patient with mitral stenosis are illustrated in Fig. 1. The rise in oxygen uptake was very similar in the two studies. The rise in the concentration of lactic acid was, however, far greater in the patient with mitral stenosis, both in the arterial and femoral venous blood, whereas the femoral venous-arterial lactic-acid difference was also greater. At the same time the femoral venous blood oxygen saturation fell to a lower level in the patient with heart disease than in the normal subject.

The oxygen saturations of the brachial arterial, femoral venous, and pulmonary arterial blood at rest and during exercise are detailed in Table V. The blood flow through the exercising legs, as estimated by the method of Donald, Wormald, Taylor and Bishop[9] is also given in this table.

The concentrations of lactic acid in the arterial blood of patients confined to bed are shown in Fig. 2. Those patients with normal hearts and lungs had a mean value of 9.17 mg./100 ml. (S.D. = 1.77 mg./100 ml.). Those with shortness of breath on mild or moderate exercise had a mean value of 10.62 mg./100 ml. (S.D. = 2.25 mg./100 ml.). Those in congestive failure had a mean value of 10.14 mg./100 ml. (S.D. = 2.04 mg./100 ml.). Although the average value for the patients with heart disease was slightly higher than that for those without heart disease, the difference could readily have arisen by chance ($t = 1.880$; $0.1 > p > 0.05$). Furthermore, the mean value for those in classification Grade IV was slightly less than that for those in Grade III.

Discussion

Steadiness of state. It is evident from the work of Bang[12] that the level of lactic acid in the blood during exercise rises steeply at first, but later declines again, even though the rate of external work remains unchanged. Our own preliminary studies in normal subjects showed that a new constant level of lactic acid in the blood may eventually be reached if exercise is continued for long periods, but that this may take more than 30 minutes to attain even with moderate degrees of activity.

It is certain, therefore, that no ultimate steady-state level of lactic acid in the blood can be reached within the space of 10 minutes of exercise. Thus, any measurements of lactic acid in the blood taken within this period must be related to the time of sampling as well as to metabolic activity. To a certain extent, therefore, the times of all such measurements must be arbitrarily chosen. However, as previously stated, our preliminary studies suggested that the maximal level of lactic acidemia usually occurred between the fifth and tenth minutes of exercise in both normal subjects and cardiac patients, and that during this period a relatively steady level of lactic acid could be expected in the arterial blood. It was for this reason

Table V. *The arterial, mixed venous, and femoral venous blood saturation at rest and during exercise. Calculated leg blood flow during exercise*

Case number	*Group*	Sa_{O_2}		$S\bar{v}_{O_2}$		Sfv_{O_2}		*Fem. A* V_{O_2}		$\dot{Q}$ *leg exercise*
		Rest	*Ex.*	*Rest*	*Ex.*	*Rest*	*Ex.*	*Rest*	*Ex.*	
					Normal Subjects					
A807	A	99	100	68	64	51	49	7.1	7.4	2.5
A822	A	97	97	84	58	87	37	2.0	11.4	5.2
A832	A	100	100	85	40	90	33	1.6	11.0	7.0
A774	B	97	97	74	—	79	35	2.8	10.5	5.7
A774	B	97	97	74	—	88	29	1.5	11.5	7.7
A810	C	99	100	—	—	82	42	3.3	11.5	4.0
A833	C	99	97	—	—	82	20	3.6	16.7	6.5
A920	D	97	98	81	63	—	—	—	—	—
					Cardiac Patients					
A812	A	96	97	60	22	68	12	6.3	18.5	1.6
A824	A	96	97	61	38	59	23	6.1	12.4	1.8
A828	A	97	97	66	30	80	25	2.5	11.3	5.4
A834	A	96	97	59	40	48	16	10.5	18.3	1.2
A836	A	92	95	59	10	58	0	7.0	20.2	3.7
A840	A	97	93	67	31	75	15	4.5	16.4	2.9
A842	A	98	96	71	44	82	31	2.9	12.0	6.5
A850	A	90	88	30	19	40	9	10.6	17.2	0.9
A854	A	99	98	70	34	76	24	4.7	15.9	3.0
A857	A	99	98	77	31	88	18	1.7	13.9	7.0
A865	A	96	95	73	35	68	23	5.1	13.1	5.6
A875	A	99	98	76	20	77	11	4.5	20.3	8.3
A780	B	98	93	31	—	54	7	8.0	15.8	0.8
A785	B	98	98	73	—	74	29	4.1	12.1	3.0
A787	B	87	81	59	—	65	59	4.7	11.4	1.8
A791	B	99	100	61	—	75	29	4.3	12.2	3.5
A795	D	97	97	52	34	—	—	—	—	—
A801	D	98	97	70	43	—	—	—	—	—
A803	D	96	93	75	37	—	—	—	—	—
A821	D	97	97	55	33	—	—	—	—	—
A917	D	95	95	69	29	—	—	—	—	—
A927	D	99	99	77	43	—	—	—	—	—
A929	D	98	98	68	22	—	—	—	—	—
A934	D	98	97	76	34	—	—	—	—	—

Sa_{O_2} = Arterial oxygen saturation (%). Sfv_{O_2} = Femoral venous oxygen saturation (%). $S\bar{v}_{O_2}$ = Mixed venous oxygen saturation (%). $\dot{Q}$ leg = Estimated blood flow in leg (L./min.).

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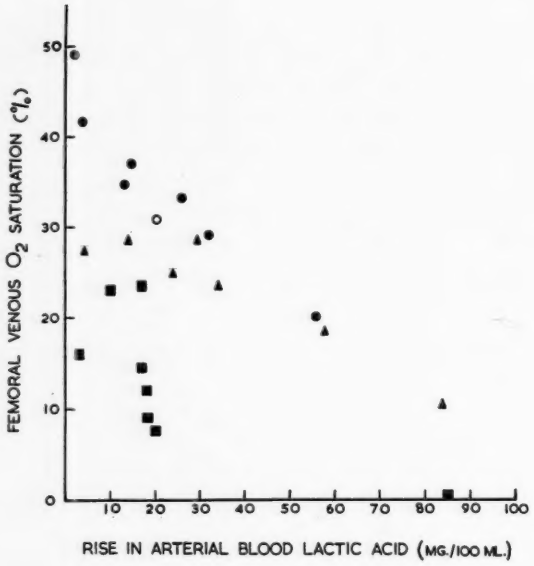

Fig. 4. The relationship of the mean femoral venous blood oxygen saturation to the mean rise in lactic-acid concentration in arterial blood during the fifth to tenth minutes of exercise. Symbols as in Fig. 3.

that measurements of lactic acid during exercise were made at the sixth, eighth, and tenth minutes.

In fact, the average values of lactic-acid concentration in brachial arterial blood in all subjects studied were 34.9 mg./100 ml. at 6 minutes, 37.2 mg./100 ml. at 8 minutes, and 36.8 mg./100 ml. at 10 minutes. The femoral venous samples in Groups A, B, and C had average values of 41.6, 43.9, and 42.7 mg./100 ml. at 6, 8, and 10 minutes, respectively. Thus, the expectation of a reasonably steady level of concentration of lactic acid in the blood over the second half of the 10-minute period of exercise appears to have been largely justified. Measurements of oxygen uptake made at the beginning and end of this period provide a useful check on the constancy of the level of exercise at this time. The average values for all subjects were 473 ml./min./M.^{2} at 4 to 5 minutes, and, again, 473 ml./min./M.^{2} at 9 to 10 minutes.

Total oxygen uptake and lactic acid. The relationship between the rise in the concentration of lactic acid in arterial blood and the rise in total body oxygen uptake during exercise is plotted in Fig. 3. Note that the oxygen uptake is standardized for body size, since the level of lactic acid in the arterial blood will also be affected by body size. In the case of the normal subjects and the patient with a normal cardiac-output response the relationship between these values appears to be curvilinear, particularly since it must pass through the point of origin (Fig. 3,*A*). The concentration of lactic acid in the arterial blood increases but little with slight exercise, and then more abruptly as the exercise becomes heavier. The patients with heart disease differ from the normal subjects in that, with only a few exceptions, there is a greater increase in the concentration of lactic acid in arterial blood for an equal rise in oxygen uptake, particularly at the lower levels of exercise (Fig. 3,*B* and *C*). The patients with the greatest degree of limitation of cardiac output during exercise are those who show the greatest difference from the normal relationship.

Femoral venous blood saturation and lactic acid. The relationship found between the rise in the concentration of lactic acid in the arterial blood and the level of oxygen saturation in the femoral venous blood during the latter half of exercise is plotted in Fig. 4. In the subjects with normal cardiac outputs the concentration of lactic acid in the arterial blood increases almost

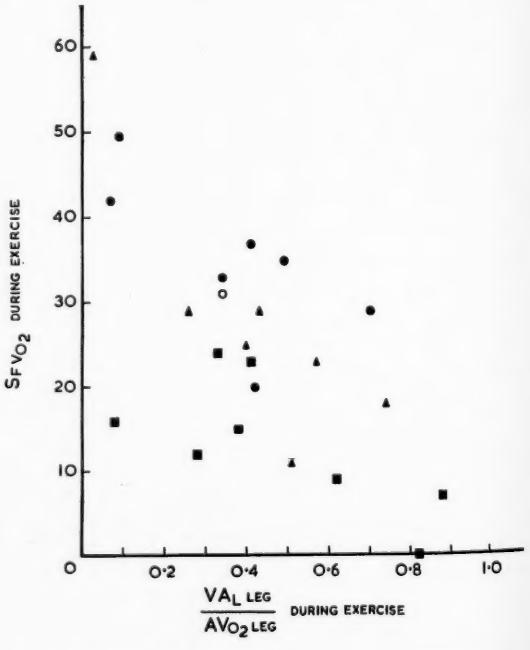

Fig. 5. The relationship of the mean femoral venous blood oxygen saturation to the ratio VA_L/AVo_2 (milligrams of lactic acid produced per milliliter of oxygen used) in the leg between the fifth and tenth minutes of exercise. Symbols as in Fig. 3.

linearly as the femoral venous saturation falls below 40 per cent. The values in the patients with heart disease again depart from the normal relationships to an extent which increases with increasing limitation of the cardiac output. Thus, the greater the disability the less is the rise in the concentration of lactic acid in the arterial blood at any given level of femoral venous blood saturation. It is to be appreciated that in order to attain the lower levels of femoral venous saturation the subjects with normal or only moderately impaired cardiac-output responses have to carry out considerable exertion, whereas the patients with severe heart disease attain these levels with relatively light exercise.

Total oxygen uptake, femoral venous blood saturation, and lactic acid. On the basis of the assumption that the arterial concentration of lactic acid is a fair measure of the production of lactic acid, the data so far presented suggest, not surprisingly, that the production of lactic acid depends on the degree of exercise and increase in oxygen utilized, and also on the degree of fall in oxygen tension, in the exercising muscle. In order to combine these two parameters in an attempt to measure the production of lactic acid it is necessary to know the influence of a fall in muscle oxygen tension on the production of lactic acid. An estimate of the ratio of the production of lactic acid to the consumption of oxygen in the exercising limbs under varying conditions can be made as below:

$$\text{Leg blood flow } (\dot{Q}\ \text{leg}) = \frac{\text{O}_2 \text{ consumption by legs } (\dot{V}_{O_2}\ \text{leg})}{\text{AV oxygen difference in legs } (AV_{O_2}\ \text{leg})}$$

Also

$$\dot{Q}\ \text{leg} = \frac{\text{Rate of production of lactic acid in legs } (\dot{M}_L\ \text{leg})}{\text{VA lactic acid difference in legs } (VA_L\ \text{leg})}$$

Thus

$$\frac{\dot{V}_{O_2}\ \text{leg}}{AV_{O_2}\ \text{leg}} = \frac{\dot{M}_L\ \text{leg}}{VA_L\ \text{leg}}$$

And

$$\frac{\dot{M}_L\ \text{leg}}{\dot{V}_{O_2}\ \text{leg}} = \frac{VA_L\ \text{leg}}{AV_{O_2}\ \text{leg}} \qquad (1)$$

The two values in the latter ratio (1) are directly measured, and the ratio expresses milligrams of lactic acid diffusing into the blood of the leg from the exercising muscle per milliliter of oxygen consumed by the leg. The ratio is an over-all value for all of the tissues of the limb and is not strictly confined to the metabolism of the muscles. The muscles, however, certainly account for almost all of the metabolism under exercising conditions; and, furthermore, even if there were a considerable increase in blood flow through relatively non-metabolizing zones, it would have little effect on the ratio. Thus, the ratio is analogous to the respiratory exchange ratio of expired air which is unaffected by the magnitude of dead-space ventilation.

The values of this ratio (femoral VA_L/ femoral AV_{O_2}) during exercise are given in Table II. The ratio during rest has not been calculated, in view of the degree of error in the estimation of lactic acid in relation to the resting gradients. The milligrams of lactic acid produced per milliliter of oxygen consumed in the leg during exercise are plotted against the femoral venous saturation in Fig. 5. Once again the two variates are not entirely independent, but their mathematical relationship would be such as to produce a positive correlation instead of the negative one observed. A most interesting correlation is the considerable increase in the production of lactic acid (from < 0.1 mg. to > 0.8 mg. per milliliter of oxygen) as the femoral

venous saturation falls (from > 50 to < 10 per cent). It will be noted that even normal and mildly disabled patients with heart disease show this increase in the production of lactic acid per unit of oxygen consumed at higher levels of exercise and lower levels of femoral venous saturation. It will also be noted that the greater is the impairment of the increase in cardiac output the lower are the levels of femoral venous blood saturation at which the production of lactic acid per unit of oxygen consumed increases. It is tempting to suggest that this may be due to enzymatic adaptations. However, in previous studies[9] of blood flow in the leg under these conditions, evidence was given which suggests that the skin blood flow to the leg increases considerably during leg exercise in normal subjects, and that it is only in the most disabled subjects that the skin blood flow to the leg remains at extremely low levels during leg exercise. *Thus, it is probable that saturation of the blood leaving the exercising muscle is of the order of the femoral venous saturation in only those patients with Grade III impairment of the cardiac-output response to exercise.* However, this data can still be used to give an approximate estimate of the production of lactic acid at different levels of femoral venous saturation. The regression equation for the prediction of lactic-acid production as calculated from the data illustrated in Fig. 4 is shown in Equation (2) below, where $S^{ex}_{FVO_2}$ is the oxygen saturation of the femoral venous blood.

If we wish to use this regression equation to calculate the amount of lactic acid produced in the exercising muscle during exercise, then it would appear reasonable to employ the increase in the concentration of lactic acid in the arterial blood as a measure of the lactic acid produced by the exercising muscles, and the increase in oxygen uptake as a measure of the oxygen consumed by the exercising muscles. The equation then becomes that shown in Equation (3) below. Thus, we now have a relationship which makes allowances for both the increase in metabolism and the effect of the muscle oxygen tension on this metabolism. It is unfortunate that neither femoral venous blood oxygen tension nor pH was measured, but, nevertheless, in the range of blood oxygen saturation under consideration the relationship of saturation to oxygen tension is almost linear, provided that changes in pH are not of a very variable degree.

When the increase in the concentration of lactic acid in arterial blood is plotted against the derivation of increase in total body oxygen uptake and femoral venous blood saturation described above, a striking correlation is obtained (correlation coefficient, r = +0.91) with all subjects and patients studied (Fig. 6). There is no longer any important distinction between the normal subjects and the patients with varying degrees of cardiac disability. Although more precise studies are needed, there is at present no definite evidence that there is any fundamental difference

$$\frac{\dot{M}_L \text{ leg}}{\dot{V}_{O_2} \text{ leg}} \text{ (mg. lactic acid per ml. } O_2 \text{ used)} = 0.69 - 0.011\, S^{ex}_{FVO_2} \qquad (2)$$

$$\frac{\text{Increase of arterial lactic-acid concentration during exercise}}{\text{Increase of } \dot{V}_{O_2}} = 0.69 - 0.011\, S^{ex}_{FVO_2}$$

Bring $S^{ex}_{FVO_2}$ to unity/100 and rearrange:

$$\text{Increase of arterial lactic acid concentration} = \text{Increase of } \dot{V}_{O_2} \left(\frac{63 - S^{ex}_{FVO_2}}{100}\right) \qquad (3)$$

in the metabolism related to the production of lactic acid in exercising muscles in normal subjects and that in patients with heart disease.

In Fig. 6 it will be noted that 3 patients with Grade III impairment of the cardiac-output response appear to have higher levels of arterial lactic acid than the general correlation would suggest. It is of interest that these 3 subjects are the only ones in the whole series who had femoral venous blood saturations below 10 per cent during exercise. It has been shown previously that the regional venous blood saturation of the whole arm[14] and of the splanchnic region[18] may fall to levels well below 40 per cent (as low as 10 per cent) in such patients during exercise. It is possible that under these conditions lactic acid may be produced in increased quantities in nonexercising muscles and even in other tissues.

Concentration of lactic acid in arterial blood and production of lactic acid in exercising limbs. It has been assumed by many workers that these values are reliably related. The results of this study allow some further analysis of this assumption. The amount of blood flowing through the exercising legs, as estimated by the method of Donald and associates,[9] is shown in Table V. Because this estimate (admittedly, approximate) is of considerable importance in this context, it is worth briefly considering its validity. It is calculated by the Fick principle as follows:

$$\dot{Q} \text{ exercising legs} = \frac{\dot{V}_{O_2} \text{ leg at rest} + \text{Excess total } \dot{V}_{O_2} \text{ exercise}}{AVo_2 \text{ exercising legs}}$$

The oxygen uptake of the legs in the resting state has been calculated by multiplying the estimated resting leg blood flow by the measured resting femoral A-V_{O_2} difference. The resting leg blood flow has been calculated from estimations of total leg blood flow at rest by plethysmography. The values of resting leg blood flow in normal subjects and in cardiac patients with varying degrees of impairment of resting cardiac output used in these calculations[9] have been gratifyingly close to recent unpublished measurements of leg blood flow by indicator dilution techniques. Even quite considerable errors in the estimation of oxygen uptake in the resting leg, which are unlikely, will cause only small errors in the exercising blood flow values.

During supine leg exercise on a bicycle ergometer the amount of work performed by muscles outside the leg is remarkably small, and the assumption that almost all of the excess total body oxygen uptake (excess $\dot{V}_{O_2}$ exercise) is used in the legs is a reasonable one. However, the oxygen consumed by the iliopsoas and the respiratory muscles will cause a slight overestimate of the blood flow in the leg. With regard to the exercising AV_{O_2} difference the assumption is made that the femoral AV_{O_2} difference is truly representative of all of the venous blood draining from the exercising leg.

Multiplying the estimated blood flow in the leg ($\dot{Q}$ leg, Table V) by the femoral lactic acid VA difference gives an approximate measure of the rate of diffusion of lactic acid into the blood flowing through the legs ($\dot{M}_L$, Table II) during exercise. Again it is assumed that the femoral lactic acid VA difference is representative of that in all of the blood draining from the legs.

It is now possible to relate this calculated rate of diffusion of lactic acid into the blood flowing through the legs to the rise in the concentration of lactic acid in arterial blood during exercise (see Fig. 7). There is a direct relationship both in normal subjects and in all patients with varying grades of cardiac disability. It should be noted that these two variates are again not entirely independent, the concentration of lactic acid in arterial blood being employed in the determination of the femoral venous–arterial lactic-acid concentration difference. However, their mathematical relationship would be such as to produce a negative correlation, in contrast to the positive correlation observed. It should be emphasized once more that, even if the determination of the rate of addition of lactic acid to the blood flowing through the exercising muscle were completely ac-

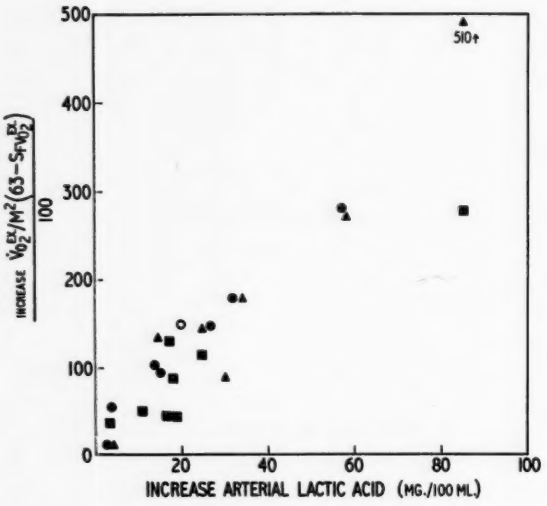

Fig. 6. The relationship of the derived value (see text) of the increase in oxygen uptake and the femoral venous blood saturation to the increase in lactic-acid concentration in arterial blood during leg exercise. Symbols as in Fig. 3.

curate, it does not necessarily measure the rate of production of lactic acid within the exercising muscles. As already stated, an abnormally low ratio of blood flow through liver (metabolism), kidney (excretion), and other tissues (diffusion and metabolism) to the blood flow through exercising muscle will prevent a normal degree of clearance of lactic acid from the blood, and, thus, levels of arterial blood will be higher and the rate of diffusion of lactic acid from exercising muscle will be decreased. If, however, a steady state could be demonstrated, including a steady concentration of lactic acid in the exercising muscles, then the true rate of production of lactic acid would be determinable.

Concentration of lactic acid in arterial blood at rest. The finding that the concentration of lactic acid in arterial blood during rest is normal in patients with severe heart disease, even when they are in congestive failure, is in agreement with that of Cotes.[1] Reports in the literature are at variance on this point and have been reviewed by Altschule.[3] These resting observations are in accordance with the present findings during exercise which suggest that the production of lactic acid, per unit of oxygen used, is not increased until the venous saturation of the region is well below 40 per cent and the muscle venous blood is below 25 per cent. In previous studies of regional venous blood saturations in patients with heart disease at rest, saturations of this low order were not found, even in the resting forearm muscle of patients with severe cardiac disability.[14,17,18]

General considerations. In the normal subjects there is only a slight rise in the concentration of lactic acid in arterial blood at the lower levels of exercise (see Fig. 3). However, as the degree of exercise increases (rise of oxygen uptake of over 300 ml./min./square meter) and the femoral venous saturation falls below 40 per cent (Fig. 3), there is a considerable rise in the production of lactic acid per unit of oxygen used by the exercising muscle (Fig. 4). Thus, the production of lactic acid rises abruptly. It was this abrupt rise in the production of lactic acid as exercise increases that led to the suggestion by Margaria, Edwards and Dill[16] that there is an "alactic" phase at the lower levels of exercise in normal subjects. In fact, there is always an increase in the production of lactic acid at even the lowest levels of exercise.

Finally, it is of interest to consider further the ratio which describes the lactic acid produced per unit of oxygen used. If one gram molecule of oxygen is considered to be "equivalent" to two grams molecule of lactic acid, as suggested by Huckabee,[2,19] then the ratio can be expressed as a pure fraction which, if all muscle metabolism

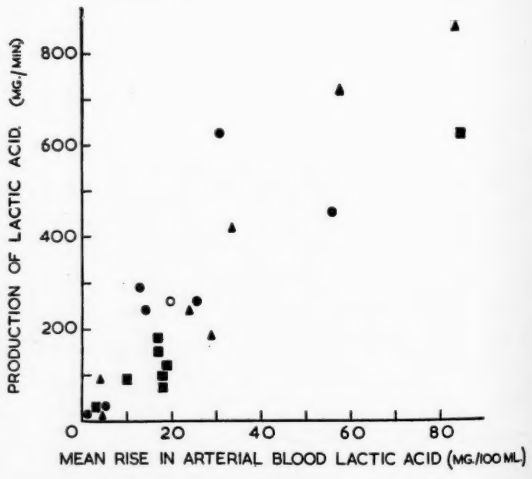

Fig. 7. The relationship of the calculated rate of production of lactic acid in the exercising legs to the rise in the lactic-acid concentration in arterial blood. Symbols as in Fig. 3.

were that of carbohydrate, would give some measure of the proportion of anaerobic to aerobic metabolism. The fractions obtained in this way are remarkably small (see Table II), considering the undoubtedly low oxygen tension in the exercising muscles in a number of these investigations. The highest figure obtained during exercise was 0.11. There is some difference of opinion concerning the oxygen equivalent of lactic acid under conditions of exercise, but the reader can make the appropriate calculations from the data in Table II. However, it has now been shown that, at rest at least, the combustion of carbohydrate accounts for only a portion of the oxygen uptake of muscle.[20] It is unwise, therefore, to draw any definite conclusions from such calculations until all possible muscle metabolites are studied simultaneously.

Summary

The concentrations of lactic acid in arterial and femoral venous blood have been measured in normal subjects and patients with heart disease during supine leg exercise on a bicycle ergometer. Measurements of oxygen uptake and of arterial, mixed venous, and femoral venous blood oxygen saturation have been made at the same time.

Patients with heart disease had a higher concentration of lactic acid in arterial blood than was found in normal subjects at similar levels of exercise and oxygen uptake. This greater rise in the concentration of lactic acid in arterial blood is related to the degree of limitation of the cardiac-output increase and to reduced blood flow in the leg and femoral venous saturation which occurred during exercise.

It has been possible to calculate the production of lactic acid per milliliter of oxygen used by the exercising legs. This value increases considerably as the femoral venous saturation (and presumably muscle oxygen tension) falls. The regression equation derived from this correlation can be used to describe the relationship between the concentration of lactic acid in arterial blood, the oxygen uptake, and the femoral venous saturation. This relationship holds good for both normal subjects and cardiac patients.

An approximate estimate has been made of the blood flow in the leg during exercise, and this has allowed the approximate order of lactic acid produced by the exercising muscles to be determined. These calculated values correlate fairly well with the concentration of lactic acid in arterial blood.

In a study of the concentration of lactic acid in the arterial blood of patients at rest in bed, the concentration in severely disabled patients with heart disease was of the same order as that in patients without cardiorespiratory disease.

Dr. O. L. Wade (now Professor) gave valuable assistance during the early stages of this work.

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The circulatory effects of hexadimethrine bromide (Polybrene) in dogs

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Hexadimethrine bromide (Polybrene) is a polymeric quaternary ammonium salt for which the empirical formula is $(C_{13}H_{30}Br_2N_2)x$. It neutralizes the anticoagulant action of heparin both in vitro and in vivo, and, according to Blumberg, Winterscheid, Dillard, Vetto and Merendino,[1] it has the advantages over protamine sulfate of uniform potency, stability, less toxicity, less hypotensive effect, and a faster action. The presently agreed anticoagulant neutralizing dose of Polybrene is 1 to 2 mg. for each milligram of injected heparin.

No toxic effects were observed when Polybrene was injected intravenously in anesthetized nonheparinized dogs in a dose range of 1 to 5 mg. per kilogram of body weight (Kimura, Young, Stein and Richards[2]). However, these workers observed that larger doses of Polybrene were often associated with moderate reduction of the systemic arterial pressure, and that very large doses of the drug, of the order of 30 mg. per kilogram of body weight, were uniformly fatal in these unheparinized animals; prior heparinization was found, however, to prevent these lethal effects until a much greater dose level was reached.

Lillehei, Sterns, Long and Lepley[3] did not observe any toxic effects of the drug when it was injected rapidly in doses up to 12 mg. per kilogram of body weight intravenously in unanesthetized heparinized dogs, whereas Weiss, Gilman, Catenacci and Osterberg[4] reported that Polybrene in a 1:1 neutralizing dose in heparinized dogs caused mild hyperpnea which increased with the rate of injection of the drug.

During clinical trials, Blumberg and associates[1] found no hypotensive effect when the drug was slowly injected intravenously in human subjects. However, Weiss and co-workers[4] observed that the slow injection of diluted Polybrene in a heparin-neutralizing dose was associated with symptoms in 14 out of 30 heparinized patients. The symptoms appeared within a few minutes of the injection and included giddiness, wheezing, coughing, choking, tightness of the chest, burning sensation in the chest, facial flushings, lumbar backache, generalized sweating, weakness,

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numbness of the arms, and cramp of the legs. Blood pressure records taken at the time of the injection showed a fall in systemic arterial pressure of 10 to 50 mm. Hg in 7 of the patients. The blood pressure recovered rapidly in these subjects.

More recently, Rothnie and Kinmonth[5] observed that the rapid injection of the drug in dogs was associated with an immediate reduction in the systemic arterial pressure. However, when slower injections of the drug were given to patients after cardiopulmonary bypass, there was no change in the systemic blood pressure.

During experiments with the extracorporeal circulation in dogs, we noticed that the rapid intravenous injection of undiluted Polybrene was immediately followed by an obvious dilatation of the right side of the heart, associated with a marked fall in systemic arterial pressure. It seemed possible that these changes might be due to pulmonary hypertension induced by the drug, and the following report describes a series of experiments designed to study the effects of Polybrene on the systemic and pulmonary circulations of the anesthetized dog.

Material and methods

Laboratory techniques. Mongrel dogs of both sexes, of which the weights ranged from 7 to 37 kilograms, were anesthetized by intravenous sodium thiopentone (20 to 25 mg./Kg. of body weight) and maintained thereafter on a cyclopropane oxygen mixture given through a closed circuit by endotracheal intubation and hand ventilation. The chest was opened by splitting the sternum, and a modified No. 9 double-lumen cardiac catheter was passed into the pulmonary artery via the right ventricle to allow pressure records and samples of blood to be taken simultaneously. Nylon catheters (2 mm. internal diameter) were passed directly into the left atrium, right atrium, and both femoral arteries, the latter to allow simultaneous arterial blood samples and pressure records. Pressures were recorded from each of these catheters by inductance manometers. The pulmonary arterial and left atrial pressures were arranged to allow direct differential records. Mean pressures were recorded by electrical integration. Zero reference point was the back of the dog in the supine position. Pressures were recorded by an ultraviolet recorder. Blood oxygen saturation was determined by a Brinkman hemoreflector, and blood oxygen capacity was measured by means of a Unicam densitometer calibrated against the method of Van Slyke. Arterial blood pH was determined according to the method of Wynn and Ludbrook.[6] Arterial pCO_2 was derived from the Singer and Hastings[7] nomogram, using the foregoing pH measurement, and the CO_2 content was measured according to the method of Van Slyke and Neill.[8] Blood transfusion was given at the time of sampling to replace the measured loss of blood.

Plan of investigation. The experiment was designed to demonstrate the circulatory effects of both the rapid and slow intravenous injections of undiluted Polybrene. All of the dogs in the three groups were heparinized by a dose of 3 mg. per kilogram of body weight.

Group I (6 dogs). After the initial procedures of anesthetization, operation, heparinization, and positioning of the various catheters, phasic and mean pressures were recorded from the various sites during a 2-minute control period. Arteriovenous blood oxygen content difference (A-V diff.) was measured at the beginning and end of this period; and at the same time, arterial pH and pCO_2 were determined. Blood oxygen capacity was measured 1 minute after the start of the control period, and this value was used for the calculation of the A-V diff. during that period and also for the A-V diff. at 1 minute after the injection of Polybrene. Fifty milligrams (5 ml.) of undiluted Polybrene was then injected into a peripheral vein within 4 to 10 seconds. Pressure records were made throughout the period of injection and continued for 5 minutes thereafter. Samples of blood were taken for measurements of A-V difference at 1 minute after the injection and again during the recovery period at 5 minutes, at which latter time the pH and pCO_2 were also determined. Blood oxygen capacity was measured during the recovery period, and the value was used for calculating the A-V diff. at that time. Two further experiments were then carried out in an identical manner with injections of 50 mg. of Polybrene on each

occasion. The control period in these two subsequent experiments was the recovery period of the preceding experiment.

Group II (4 dogs). Curarization with 5 to 10 mg. of d-tubocurarine intravenously was performed at the time of the anesthetization; otherwise the initial procedures were carried out as in the previous experiment, including the measurements and determinations during the control period, up to the point of injection of Polybrene. The undiluted drug was then infused into a peripheral vein in a dose of 50 mg. per minute for 3 minutes. Pressures were recorded during the injection of Polybrene, throughout the postinjection period for 5 minutes, and then during a 3-minute recovery period. A-V differences were determined at minute intervals during the 3 minutes of the injection and again during the recovery period. Blood oxygen capacity was measured during the second minute after the start of the injection of Polybrene, and this value was used for the calculation of the A-V differences during the infusion. The blood oxygen capacity was again determined during the 3-minute recovery period. Also measured were pH and pCO_2, at 1 minute after the start of the infusion and again during the recovery period.

Group III (7 dogs). This group of animals was used as a control experiment to demonstrate the acute effects of injections of the same volume of normal saline as in the dogs of Group I. The experimental protocol was identical to that described for the dogs of Group I, except that saline was substituted for the first and third injections of the drug, and the second injection was of 50 mg. of Polybrene.

Results

Group I. A representative record of the vascular pressures of a heparinized dog after the rapid intravenous injection of 50 mg. of undiluted Polybrene into a peripheral vein is shown in Fig. 1.

The average mean pulmonary arterial pressure during the control period was 11 mm. Hg. In all of the experiments the pulmonary arterial pressure started to increase between 4 and 10 seconds after the start of the injection of Polybrene, and an average maximal increase of 14 mm. Hg was reached after 8 to 32 seconds. The individual maximal increases in the mean pulmonary arterial pressure in all experiments are shown in Fig. 2.

The average mean femoral arterial pressure during the control period was 82 mm. Hg. In all instances the femoral arterial pressure started to fall between 6 and 14 seconds after the start of the injection and reached an average maximal reduction of 40 mm. Hg after 13 to 44 seconds. Individual maximal changes in the mean femoral arterial pressure are shown in Fig. 2. The average of the maximal changes in mean vascular pressures after the first, second, and third injections of Polybrene are presented in Table I. The average of the changes in the mean femoral and pulmonary arterial pressures after Polybrene in the first and second injections and the time relationships are shown in Fig. 3. The average percentage change in these pressures in all 18 experiments and the time relationships are presented in Table II.

The increase in pulmonary arterial pressure always preceded the fall in systemic arterial pressure by 2 to 4 seconds. The average mean left atrial pressure during

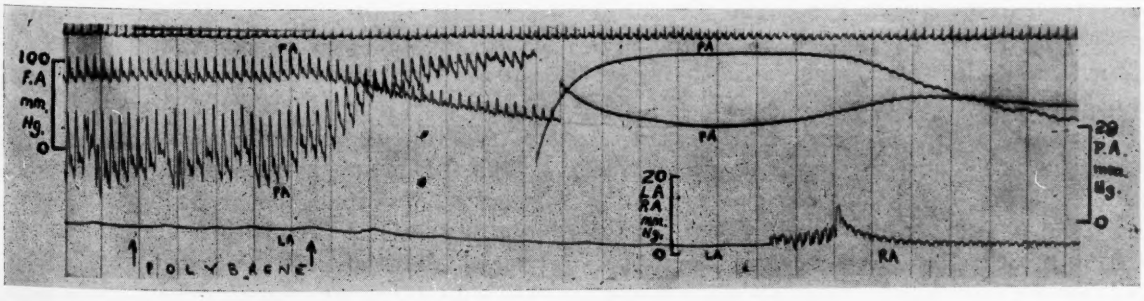

Fig. 1. A representative record of the vascular pressures of a heparinized dog after the rapid intravenous injection of 50 mg. of undiluted Polybrene.

Table I. *The circulatory effects of rapid intravenous administration of Polybrene. The average (range in parentheses) of the maximal changes in mean vascular pressures after the first, second, and third injections of Polybrene in 6 dogs*

	Control pressures (mm. Hg)				*Changes in pressure after Polybrene (mm. Hg)*			
	RA	*PA*	*LA*	*FA*	*RA*	*PA*	*LA*	*FA*
First injection of Polybrene	4 (1-7)	12 (10-17)	7 (5-11)	96 (65-143)	+1 (−1 to +9)	+11 (+6 to +17)	−2 (0 to −6)	−36 (−17 to −50)
Second injection of Polybrene	3 (0-6)	10 (9-12)	6 (5-8)	82 (72-98)	+2 (0 to +6)	+14 (+10 to +19)	−3 (−1 to −5)	−48 (−21 to −72)
Third injection of Polybrene	5 (2-10)	10 (7-13)	6 (4-8)	69 (38-100)	+3 (+1 to +7)	+15 (+10 to +23)	−3 (−1 to −5)	−36 (−10 to −55)

Table II. *The average percentage changes in PA and FA pressures after rapid intravenous administration of Polybrene, and their time relationships*

	Average percentage rise in mean pressure	*Average time to start of rise (sec.)*	*Average time to peak rise (sec.)*	*Average time to restabilization (sec.)*
Pulmonary artery	135% (50–220%)	7.6 (4–10)	19.7 (8–32)	74.4* (42–148)

	Average percentage fall in mean pressure	*Average time to start of fall (sec.)*	*Average time to peak fall (sec.)*	*Average time to restabilization (sec.)*
Femoral artery	54% (20–82%)	9.8 (6–14)	26.4 (13–44)	81 (34–220)

*On one occasion the pulmonary arterial pressure did not return to preinjection level until 9 minutes after injection. This figure was omitted when the above percentages were calculated.
The range of scatter is given in parentheses.

the control period was 7 mm. Hg. After Polybrene the mean left atrial pressure was reduced in all experiments except one, in which it did not change. The average mean left atrial pressure recorded at the peak of the rise in the pulmonary arterial pressure was 4 mm. Hg, an over-all reduction of 3 mm. Hg.

The average pulmonary arterial–left atrial pressure gradient before Polybrene was 4 mm. Hg. After the rapid intravenous injection of the drug this pressure gradient increased in all experiments. The average maximal increase was 16 mm. Hg. These results are illustrated graphically in Fig. 2. The average mean right atrial pressure during the control period was 4 mm. Hg. After injection of Polybrene, at the time of the maximum increase in pulmonary arterial pressure, the mean right atrial pressure was increased in 11 of the 18 experiments. The mean right atrial pressure was unchanged in 6 instances, and in one experiment it was reduced by 1 mm. Hg. The average mean right atrial pressure in the 11 experiments in which it increased,

recorded at the time of the maximum rise in the pulmonary arterial pressure, was 7 mm. Hg, an average increase of 4 mm. Hg.

The mean arterial oxygen saturation during the control period was 98 per cent. One minute after the injection of Polybrene, at a time when pulmonary arterial pressure was considerably elevated, mean arterial oxygen saturation was 97 per cent.

In 2 animals the injection of Polybrene was associated with an increasing degree of arterial oxygen unsaturation with successive injections.

The blood oxygen capacity during recovery after injection of Polybrene showed a mean increase of 0.44 volumes per cent as compared with the values in the control period.

The mean A-V diff. during the control period was 7.23 volumes per cent. One minute after injection of Polybrene the changes in A-V diff. were variable. In 4 of the 6 dogs the mean increase in A-V diff. was 0.25 volumes per cent. In 2 dogs there was a much greater change in A-V diff., particularly with successive injections of Polybrene. These large changes in A-V diff. were associated in these 2 animals with considerable arterial oxygen unsaturation.

In 4 of the 6 dogs the systemic arterial pH and pCO_2 were not significantly changed throughout the duration of the experiment, which included three successive injections of Polybrene. However, in one dog the arterial pH fell and the pCO_2 progressively increased with successive injections of Polybrene. These changes in this dog were associated with progressive oxygen unsaturation. In one other dog the arterial pH fell and the pCO_2 increased after the first injection, but thereafter remained unchanged.

The heart was observed closely during the period of each injection of Polybrene. Shortly after the completion of the injection considerable dilatation of the right heart was observed on every occasion; this dilatation coincided with the rise in pulmonary arterial pressure. Successive injections of Polybrene were associated with progressive increases in the size of the right heart. It was observed that the dilatation of the right heart was much slower to remit than was the elevation in the pulmonary arterial pressure.

Group II. During the control period the average mean pulmonary arterial pressure was 18 mm. Hg. During the infusion of Polybrene (50 mg. per minute for 3 min-

Table III. *The circulatory effects of slow infusion of Polybrene (50 mg. per minute for 3 minutes)*

Dog		*State and duration of injection*	*Pressures (mm. Hg)*				*Blood oxygen capacity (Vol. %)*	*Oxygen saturation (per cent)*		*A-V diff. (vol. %)*	*pH*	*pCO_2 (mm. Hg)*
Number	*Weight (Kg.)*		*RA*	*PA*	*LA*	*FA*		*Art.*	*MVB*			
1.	21.75*	Control	—	21	12	82	18.94	96	60	6.82	7.577	22
		Polybrene	—	27	12	54	17.14	97	54	7.37	7.616	18
2.	28.15	Control	9	20	13	100	17.47	93	50	7.51	7.470	26
		Polybrene	9	27	11	47	16.63	93	37	9.37	7.480	25
		Recovery	10	23	12	82	17.16	89	34	9.44	7.450	26
3.	17.35	Control	2	16	9	119	20.23	98	63	7.12	7.486	24
		Polybrene	4	19	10	100	19.05	97	57	7.62	7.480	24
		Recovery	3	16	8	78	20.52	98	58	8.20	7.476	24
4.	19.2	Control	2	16	9	77	17.36	98	72	4.51	7.370	23
		Polybrene	1	16	5	55	16.88	98	71	4.56	7.382	22
		Recovery	1	12	3	69	16.72	97	62	5.85	7.406	21

*No recovery readings or estimations were carried out on Dog 1 because of the development of cardiac asystole shortly after the end of the infusion of Polybrene.

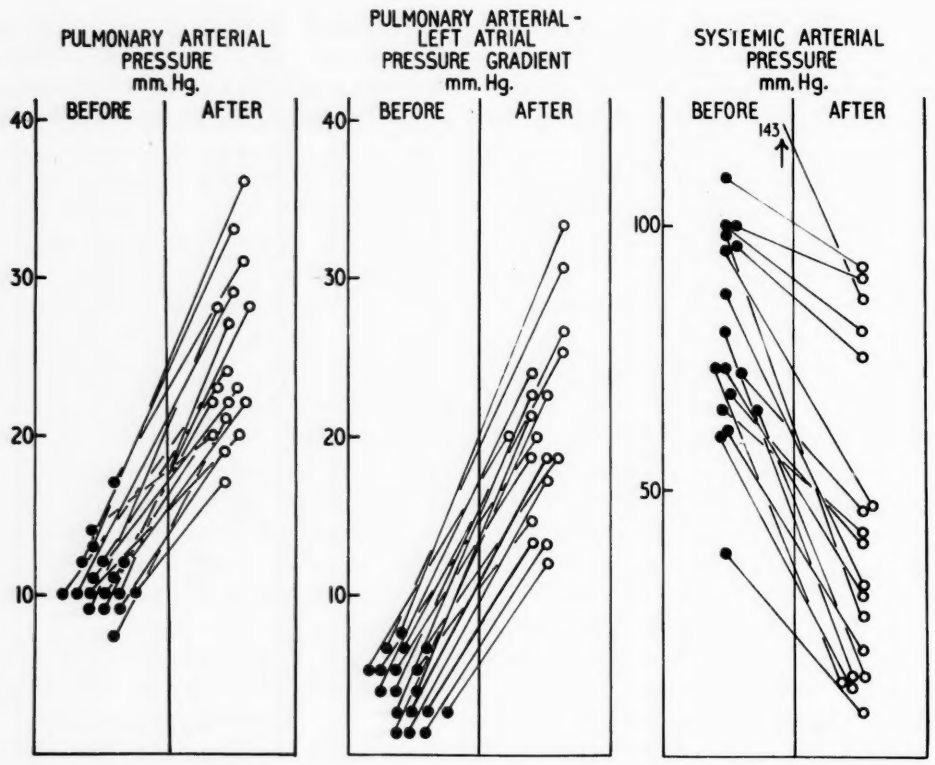

Fig. 2. Mean vascular pressures before and after the rapid intravenous injection of Polybrene.

utes), 3 of the 4 dogs showed a small increase in pulmonary arterial pressure. The increase in the mean pulmonary arterial pressure in these 3 dogs was 6, 7, and 3 mm. Hg. In the other animal (No. 4), no change was observed.

During the control period the average mean femoral arterial pressure was 95 mm. Hg. During the infusion of Polybrene the femoral arterial pressure was reduced in all 4 dogs; the mean average maximum reduction was 31 mm. Hg.

Neither right nor left atrial pressure showed any consistent trend during infusion of Polybrene as compared to the control period, and the maximum change observed was 4 mm. Hg (see Table III).

The mean arterial oxygen saturation during the control period was 96 per cent, and remained unchanged during the infusion of Polybrene.

The mean blood oxygen capacity during the control period was 18.50 volumes per cent. The blood oxygen capacity determined 2 minutes after the start of the infusion of Polybrene showed a mean decrease of 1.05 volumes per cent as compared with the values of the control period.

The mean A-V diff. during the control period was 6.49 volumes per cent. During the 3-minute period of infusion of Polybrene the A-V diff. increased in all dogs; the mean increase was 0.74 volumes per cent. In all of the dogs the systemic arterial pH and pCO_2 remained relatively unchanged throughout the experiment (see Table III).

The heart was observed closely throughout the period of infusion of Polybrene. Within 1 or 2 minutes of the commencement of infusion the right heart was noticed to be increasing in size, and, as the infusion continued, this dilatation became progressively more conspicuous until both the right ventricle and right atrium appeared to be grossly overdistended. This occurred in all 4 dogs, although the changes in the pulmonary arterial and right atrial pressures were small.

Group III. Rapid injections of 5 ml. of normal saline in 7 dogs failed to show any measurable effects on the pulmonary arterial, left and right atrial, and systemic arterial pressures. A subsequent injection of 5 ml. of undiluted Polybrene, given under the same experimental conditions as in

the dogs of Group I, consistently caused a similar rapid but transient elevation of the pulmonary arterial pressure without change in the left atrial pressure. An additional injection of 5 ml. of normal saline after the dogs had recovered from this injection of Polybrene again failed to show any change in the right or left heart pressures. This demonstrates the absence of measurable effects due to the rapid intravenous injections of 5 ml. of normal saline, although 5 ml. of Polybrene injected under identical conditions produced marked circulatory changes.

Discussion

These experiments have shown that the rapid intravenous injection of undiluted Polybrene in doses commonly used therapeutically consistently produced a considerable increase in the pulmonary arterial pressure in heparinized anesthetized open-chest dogs. This rapid but transient elevation of the pulmonary arterial pressure was reproducible in the same animal with successive injections. The pulmonary arterial–left atrial pressure gradient was considerably increased in all experiments; the left atrial pressure usually was reduced. This increase in pressure gradient could have been caused by an increase in the vascular resistance or by a very considerable increase in the right ventricular output. Since oxygen uptake was not determined, measurements of blood flow are not available. However, the following considerations suggest that the increase in pulmonary arterial pressure was due to increased resistance rather than flow. First, a considerable increase in pressure gradient across the lungs was consistently produced after Polybrene despite variable changes in the arteriovenous oxygen content difference. Secondly, the right heart showed a marked dilatation during this acute phase, concomitant with the abrupt increase in the pulmonary arterial pressure, and this dilatation was often associated with a small increase in the right atrial pressure. The occurrence of a marked fall in systemic arterial pressure a few seconds after the increase in pulmonary arterial pressure again suggests a failure of flow due, initially, to acute right heart embarrassment.

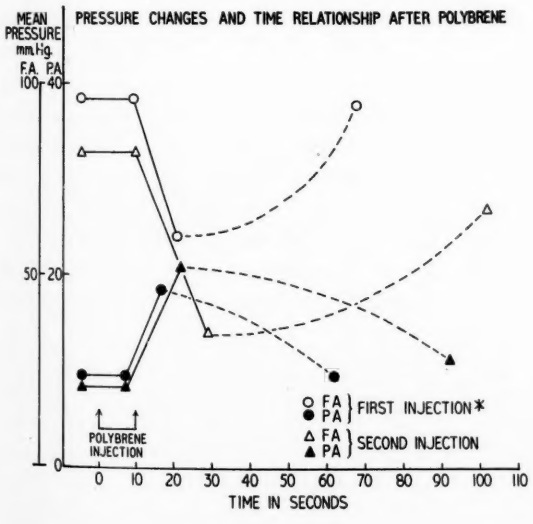

Fig. 3. The average of the changes in mean maximal systemic and pulmonary arterial pressures after the first and second rapid intravenous injections of Polybrene are plotted against time. The changes in pressure and the time relationships after the third injection are not plotted but are not substantially different from those after the second injection. *After the first injection of Polybrene in one dog the pulmonary arterial pressure did not return to normal until after 9 minutes. This exceptionally long time was omitted when calculation was made of the percentage time of restabilization after the first injection.

The control studies in which the rapid intravenous administration of the same volume of normal saline was used instead of Polybrene show that the volume effect of the injection was negligible.

The effect of continuous but much slower infusion of the drug on the pulmonary arterial pressure was much less marked, and the main effect observed was acute right heart dilatation, accompanied by a profound systemic arterial hypotension. This observation, in the light of the previous experiments with acute injections of the drug, suggests a mechanism of action that is not confined to its pulmonary vascular effects. The acute right heart dilatation accompanied by a marked fall in the systemic arterial pressure with only a small increase in the pulmonary arterial pressure suggests that myocardial performance was being influenced by either a direct toxic effect or an indirect neurohumoral mechanism. Although these effects of the drug on the pulmonary circulation have not been recorded previously, the observed reduction of the systemic arterial

pressure confirms the similar observation recently reported by Rothnie and Kinmonth.[5] The only other work which has any relevance to the present experiments is that of Weiss and co-workers,[4] who observed that the intravenous infusion of diluted Polybrene in human subjects was often accompanied by systemic arterial hypotension, dyspnea, and sensations of distress, which could possibly be explained on the basis of these findings.

Although these experiments have been carried out in the anesthetized open-chest dog, the consistency of the findings and the fact that the doses of drug were within the range of those normally used therapeutically compel the authors to advise caution in the use of this drug, particularly if it is given rapidly by the intravenous route.

Summary

1. The effects of both rapid and slow intravenous injections of undiluted Polybrene on the pulmonary and systemic circulations of anesthetized, heparinized open-chest dogs have been studied.

2. The rapid injection of 50 mg. of Polybrene was followed by an abrupt increase in the pulmonary arterial pressure, associated with a fall in the left atrial pressure, an increase in the right atrial pressure, and a reduction of the systemic arterial pressure in all of the animals studied. Successive injections of the same amount of the drug produced an identical pattern of response.

3. With slower injections the effects on the pulmonary arterial pressure were not so marked, but acute right heart dilatation was still observed.

4. The evidence from these experiments suggests that the effects of the drug are probably twofold, in that it increases the pulmonary vascular resistance at a site which, at present, is undetermined and, in addition, appears to cause acute right heart dilatation, which may be due in part to a depressant action on the myocardium.

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Pulmonary and renal circulatory adjustments to the upright posture in patients with mitral valvular disease

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Orthopnea, i.e., breathing associated with effort in the recumbent position, is a common symptom in left heart disease as a consequence of disordered pulmonary circulatory hemodynamics. Even if respiratory and cerebral factors have been implicated as the origin of orthopnea, much interest has been directed to define the pulmonary hemodynamic derangement.[1] Thus, it still remains disputed whether orthopnea is caused by an increase in the pulmonary blood volume or by an increase in the pulmonary blood pressures leading to extravasation of fluid, as the cranial part of the body is lowered. Also, a possible change in renal hemodynamics and the renal handling of water and electrolytes, leading to retention of fluid, must be considered. In the present report the orthostatic circulatory changes are described in patients with mitral valvular disease. The cardiac output, the cardiopulmonary blood volume, and pressures in the pulmonary and systemic circuits were determined in patients in the recumbent posture (180 degrees) and when tilted to 45 or 60 degrees from the horizontal. In addition, the glomerular filtration rate, the renal blood flow, and the urinary excretion of sodium were measured simultaneously. The patients were selected to represent varying degrees of heart involvement, ranging from those who were virtually free of symptoms to those with chronic congestive failure.

Material

Ten patients with mitral valvular disease were selected for study, 8 women and 2 men. Aortic valvular disease was present in Patient No. 473. Six had sinus rhythm, and 4 had atrial fibrillation. The heart size[2] ranged between 400 and 1,060 ml. per square meter of body surface area. When grouped according to the New York Heart Association,[3] 2 of the patients were in Group II, 7 in Group III, and 1 in Group IV. The clinical data are listed in Table I.

Methods

All patients were studied in the morning, recumbent, and in the postabsorptive state. Sodium Amytal, 0.1 Gm., was administered 2 hours before the start of the study. The pulmonary artery was catheterized according to Cournand,[4] and an indwelling needle was placed in the brachial artery.

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Table I. *Clinical data in 10 patients with rheumatic heart disease*

Case number	*Sex*	*Age (yr.)*	*Group (N. Y. Heart Assn.*[3]*)*	*Rhythm*	*Heart size (ml./M.*^{2} *BSA)*	*Right heart failure*	*Digitalis*	*Diagnosis*	*Orthopnea*
567	F	32	III	SR	500	−	+	MS	+
597	F	49	III	AF	630	−	+	MS, MI	+
632	F	36	II	SR	500	−	+	MS, op	−
349	F	50	III	AF	730	−	+	MS, MI	+
408	F	40	III	SR	400	−	+	MS	−
473	M	21	III	SR	750	−	−	AI, MI	−
475	F	51	III	AF	800	−	+	MI	+
387	M	31	IV	AF	1,060	+	+	MS, MI	+
801	F	28	III	SR	580	+	+	MI	+
793*	F	28	II	SR	400	−	−	MS	−

*Tilted head down 30 degrees.
SR: Sinus rhythm. AF: Atrial fibrillation. MS: Mitral stenosis. MI: Mitral insufficiency. AI: Aortic insufficiency. MS, op: Mitral stenosis, operated by mitral commissurotomy.

The pressures in the pulmonary circuit were measured, including the pulmonary arterial wedged pressure (PCV).[5] Then the patient was allowed to rest for 30 minutes. Thereafter, the cardiac output was determined using the direct Fick principle, with simultaneous sampling of blood from the pulmonary and brachial arteries and collection of expired air in a Tissot spirometer for 2 minutes. Pressures were then recorded again, and the catheter was advanced to the "wedged" position. During continuous registration of pressures the patient was tilted to a position of 45 or 60 degrees from the horizontal (head up) and left there for about 30 minutes.[6] After the patient had been in the tilted position for 10 minutes, the catheter was withdrawn to the pulmonary artery, as judged from the pulse contour. The cardiac output was determined again, the catheter withdrawn to the right atrium, and, under pressure recording, the patient tilted back to the horizontal position. In some studies, measurements were repeated after the patient had been in the horizontal position for 30 minutes.

One patient (No. 793) was tilted 30 degrees head down. No symptoms appeared in this position. The same measurements as in the other studies were made.

In 7 patients the cardiac output was also determined by the Stewart-Hamilton technique, and the total and the cardiopulmonary blood volumes[7] in the recumbent and in the upright postures were calculated.

In all patients the procedure was combined with the determination of renal clearances for para-aminohippurate and inulin, and the excretion of sodium was also determined. The clearance periods were generally between 15 and 30 minutes. The details of these techniques have been described before.[8]

The blood gases were analyzed according to Van Slyke,[9] and the expired air according to Haldane.[10] Blood pressures were

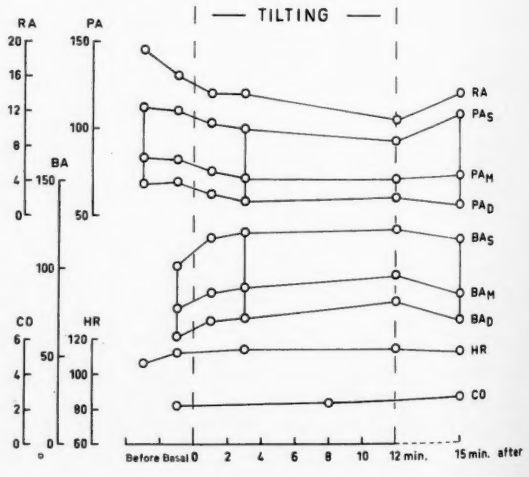

Fig. *1*. This graph shows the effect of tilting (head up 60 degrees) in a patient with mitral valvular disease in right heart failure (Case 387). *RA* = right atrial, *PA* = pulmonary arterial, *BA* = brachial arterial pressures, in mm. Hg. *CO* = cardiac output, in liters per minute; *HR* = heart rate.

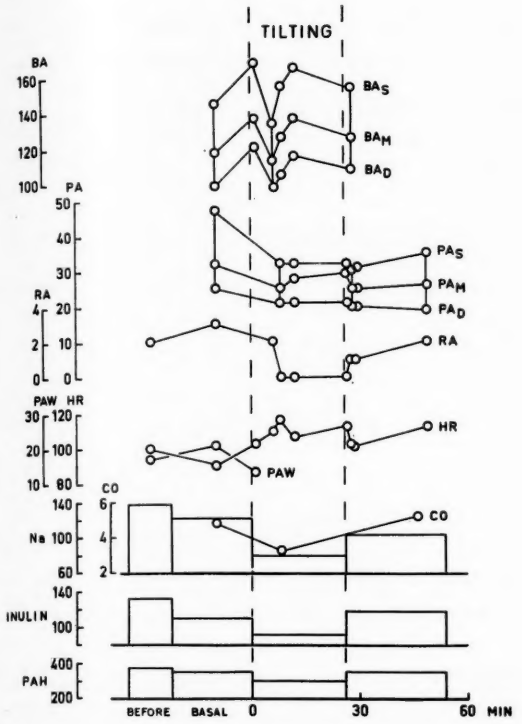

Fig. 2. This graph shows the effect of tilting (head up 60 degrees) in a patient with mitral valvular disease without evidence of right heart failure (Case 475). *BA* = brachial arterial, *PA* = pulmonary arterial, *RA* = right atrial, and *PAW* = pulmonary arterial wedged pressure, in mm. Hg. *HR* = heart rate; *CO* = cardiac output, in liters per minute. *Na* = urinary excretion of sodium. *Inulin* clearance, and the renal clearance of *PAH* (para-aminohippurate).

registered with electromanometers, either the Hansen and Warburg capacitance manometer[11] or an Elema strain gauge, and inscribed on an Elema electrocardiograph. Mean pressures were calculated from electrically integrated curves.

As reference point for the pressures, the horizontal level 5 cm. below the angle of Louis was used in the recumbent position, and the horizontal level about 3 cm. above the apex beat was used in the tilted position. The manometers were adjusted to correspond to both of these points when the pressures were continuously recorded during the change in the position of the patients.

Results

The values for blood pressures and blood flow obtained when the patients were in the recumbent and upright positions are given in Table II. The patients are divided into three groups according to the derangement of the circulation and the severity of the heart disease. The first group contains 3 patients with moderately elevated pulmonary pressures (Nos. 567, 597, and 632) and almost normal cardiac outputs (arteriovenous oxygen difference below 50 ml./L. of blood). The second group contains 4 patients with elevated pulmonary pressures (pulmonary wedged pressure above 20 mm. Hg), low cardiac outputs (Nos. 349, 408, 473, and 475) (arteriovenous oxygen difference above 50 ml./L. of blood), and no signs of right heart failure as judged either clinically or from the level of the right atrial pressure. Finally, the third group consists of 2 patients with clinical signs of right heart failure. Both had very high pulmonary pressures, but the blood flow was normal in one and low in the other. The patient who was tilted head down (No. 793) is presented last.

On the whole, the right atrial and pulmonary arterial wedged pressures decreased. This was most marked in the third and second groups, and less in the first, wherein some patients even had virtually unchanged filling pressures. The pulmonary arterial pressure decreased slightly in some of the patients in the second and third groups but was otherwise unchanged, and

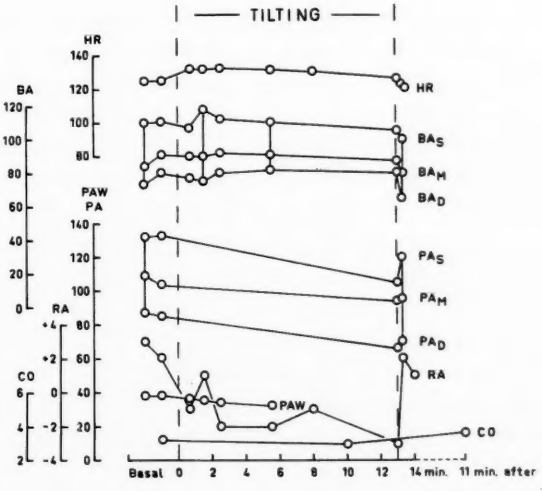

Fig. 3. This graph shows the effects of tilting (head up 60 degrees) in a patient with mitral valvular disease with marked pulmonary hypertension (Case 408). *BA* = brachial arterial, *PA* = pulmonary arterial, *RA* = right atrial, and *PAW* = pulmonary wedged pressure, in mm. Hg. *HR* = heart rate; *CO* = cardiac output, in liters per minute.

Table II. *Blood flow and blood pressures in 10 patients with mitral valvular disease*

Case number	*Heart rate*		*A-V O_2 difference (ml./L.)*		*Cardiac output (L./min.)*		*Stroke volume (ml./beat)*		*Right atrium*	
									M	
	R	*T*	*R*	*T*	*R*	*T*	*R*	*T*	*R*	*T*
567	71	82	36	48	6.5	4.9	91	60	0	1
597	85	118	54	85	4.3	2.7	51	23	1	—
632	102	130	35	42	7.0	6.4	79	66	1	1
349	72	65	62	83	2.6	2.1	36	32	4	—
408	121	130	56	67	3.2	3.0	26	23	1	−3
473	108	107	56	61	5.5	4.9	51	46	3	−2
475	91	112	54	75	4.8	3.4	53	30	3	0
387	112	114	112	110	2.2	2.4	20	21	16	11
801	90	90	49	49	6.0	6.0	67	67	5	5
793*	70	86	34	37	5.5	5.7	79	66	2	0

*Tilted head down 30 degrees. R = recumbent, and T = tilted (head up 60 degrees) position. S = systolic, D = diastolic, and

the brachial arterial pressure usually increased. The pulse pressure, both in the pulmonary and systemic circulations, usually decreased. The systemic arterial pressure usually increased.

In all patients except the 2 who were in right heart failure the cardiac output decreased when the upright position was taken. This was reflected by an increase in arteriovenous oxygen difference. The heart rate likewise increased, and the stroke output decreased markedly. In contrast, in the 2 patients in right heart failure the cardiac output, the arteriovenous oxygen difference, the heart rate, and the stroke volume did not change.

Table III contains the data obtained by the dye method. The total blood volume was definitely increased in 1 case (No. 387), a patient who was in right heart failure. The cardiopulmonary blood volume decreased in 3 cases (Nos. 349, 473, and 387), being essentially unaltered in the other 4 cases. The fall in cardiopulmonary blood volume was observed in 3 out of 4 instances, where this volume constituted more than 20 per cent of the total blood volume.

Table IV contains the values for renal plasma flow, glomerular filtration rate, and excretion of sodium. In the patients who were tilted head up the renal plasma flow, glomerular filtration rate, and excretion of sodium decreased, whereas in the patient tilted head down they tended to increase. The differences in the various circulatory parameters are shown in Table V.

Fig. 1 shows the course of events in one patient (No. 387) with right heart failure, Fig. 2 in one patient (No. 475) without heart failure, and Fig. 3 in one patient (No. 408) with marked pulmonary hypertension.

Discussion

The change from the horizontal to the upright position leads to a redistribution of blood volume and blood flow in the circulatory system for maintaining homeostasis. The decrease in venous return is reflected by a fall in the cardiac output and a rise in the heart rate.[6,12,13,32] At this stage, compensatory mechanisms enter the circulatory system to maintain an adequate cerebral blood flow.[14,15] Blood flow through other regions of the body is reduced; part of the blood volume is redistributed to the central venous channels as arterial and venous constriction ensues. Such homeostatic mechanisms are reinforced in the "passive" standing posture, and, when inadequate, the subject may faint, especially if the total blood volume is lowered for some reason. Indeed, physically trained individuals with a blood volume of good size generally show fewer reactions to orthostasis than do those not physically fit.

It has been demonstrated that veno-

Blood pressures (mm. Hg)									
Pulmonary wedge		*Pulmonary artery*				*Brachial artery*			
M		*S/D*	*M*	*S/D*	*M*	*S/D*	*M*	*S/D*	*M*
R	*T*	*R*		*T*		*R*		*T*	
19	15	42/18	27	37/22	28	95/56	73	106/78	89
17	17	39/21	27	36/23	28	165/106	127	167/128	145
14	15	36/17	26	44/19	31	134/61	83	141/72	95
23	17	54/17	26	29/13	19	140/95	112	137/100	121
38	32	133/85	104	105/66	94	111/80	91	105/80	87
28	17	47/22	34	26/10	21	140/75	100	155/73	103
21	13	47/25	32	32/21	28	144/98	117	159/110	131
—	—	110/69	82	93/60	71	101/61	77	122/81	96
36	24	75/33	50	74/33	50	132/83	101	124/80	97
—	—	18/5	11	16/5	10	105/62	78	100/55	70

M = mean, pressures.

Table III. *Cardiac output, total blood volume, mean cardiopulmonary circulation time, cardiopulmonary blood volume, and hematocrit in 8 patients with mitral valvular disease*

Case number	*BSA*	*Hct (%)*		*TBV/1.73 M.²*		*CO*		*Mct*		*CPV/1.73 M.²*		*CPV/TBV (%)*	
		R	*T*	*R*	*T*	*R*	*T*	*R*	*T*	*R*	*T*	*R*	*T*
567	1.59	36	36	5.10	4.86	5.17	4.04	6.7	11.5	0.62	0.84	12.2	17.2
597								18.2	19.9				
632	1.49	38	37	4.85	4.66	5.49	4.34	7.5	8.7	0.80	0.73	16.5	15.7
349	1.39	44	44	6.94	6.13	3.80	3.30	24.0	21.4	1.87	1.46	27.0	23.9
408	1.43	42	40	4.92	4.51	3.36	2.92	13.1	15.0	0.88	0.88	17.9	19.6
473	1.81	36	36	6.57	6.81	4.78	3.98	22.8	22.0	1.74	1.40	26.5	20.6
475	1.77	40	40	5.34	5.98	4.39	3.20	21.3	28.2	1.53	1.47	28.6	24.6
387	1.64	46	46	7.58	7.74	2.38	2.12	37.9	32.4	1.58	1.20	20.8	15.5

R = recumbent, and T = tilted position (head up). CO: Cardiac output (liters/minute). TBV: Total blood volume (liters). Mct: Mean cardiopulmonary circulation time (seconds). CPV: Cardiopulmonary blood volume (liters) by the dye method. Hct: Hematocrit. BSA: Body surface area (square meters).

Table IV. *The renal clearance of PAH (para-aminohippurate) and inulin (in ml. per minute), and the urinary excretion of sodium (in mEq. per liter) in 8 patients with mitral valvular disease*

Case number	*PAH*			*Inulin*			*Na^+ excretion*		
	R	*T*	*Rec*	*R*	*T*	*Rec*	*R*	*T*	*Rec*
597	246	188	258	73	51	85	32	13	26
632	352	259	408	113	89	104	268	161	225
408	212	197	202	79	75	71	16	18	26
473	330	291	335	103	93	100	157	133	164
475	358	293	353	121	92	118	130	81	104
387	94	84	78	68	59	53	—	—	—
801	243	267	389	44	47	56	85	53	92
793	453	474	578	97	100	129	285	372	502

R: Recumbent. T: Tilted (head up). Rec: Recumbent after tilting.

Table V. Statistical analysis of differences (tilted-recumbent position) on blood flow, blood pres- (crh) and in all patients (after the addition of 2 patients with right heart failure [rhf])

	Heart rate		*A-V O_2 difference (ml./L.)*		*Cardiac output (L/min.)*	
	crh	*rhf*	*crh*	*rhf*	*crh*	*rhf*
n_d	7	9	7	9	7	9
M_d	13.4	10.7	15.4	11.8	−0.93	−0.72
SD_d	14.7	13.9	9.27	10.8	0.58	0.65
SE_d	5.5	4.63	3.50	3.61	0.22	0.22
t	2.41	2.31	4.40	3.27	4.23	3.27
p	0.1–0.05	0.05	0.01–0.001	0.02–0.01	0.01–0.001	0.02–0.01

	BA mean		*Mct (sec.)*		*CPV/1.73 (L.)*	
	crh	*rhf*	*crh*	*rhf*	*crh*	*rhf*
n_d	7	9	7	8	6	7
M_d	9.7	9.2	1.87	0.96	−0.11	−0.15
SD_d	7.80	8.93	3.20	3.92	0.23	0.24
SE_d	2.94	2.98	1.21	1.39	0.09	0.09
t	3.30	3.09	1.55	0.69	1.17	1.69
p	0.02–0.01	0.02–0.01	0.2–0.1	0.6–0.5	0.3	0.2–0.1

motor tone is increased in small segments of the venous system during a "passive" tilting, and it is believed that this as well as the ability to maintain central venous pressure after tilting reflect an over-all increase in peripheral venous vascular tone.[21,22] Tilting and the Valsalva maneuver,[23,24] as well as positive pressure breathing,[25] tend to reduce venous return and thus lower the cardiac output. The resultant drop in blood pressure is partially or completely corrected for by widespread arteriolar constriction with an increase in the peripheral arterial resistance. Also, widespread peripheral venous constriction will lead to shifting of the blood to the central venous vessels, making it available to the heart for maintaining the output.[26] Thus, for sustaining arterial blood pressure, both arterial and venous peripheral constriction become important—the former for increasing resistance and the latter for maintaining the cardiac output.

The reduction in blood flow through different areas of the circulatory system, such as the kidney[16,17] and the liver,[18] in the tilted position has been amply demonstrated in man. The pulmonary blood volume has been implicated[19] as a major participant in the regional shift in blood volume. Indirect evidence supports the assumption of a marked reduction in volume[20]; the same applies to the few direct measurements of the intrathoracic blood volume which have been reported.[6]

The present results show that these considerations, which are based on hemodynamic studies in normal individuals, also are applicable to patients with mitral valvular disease inasmuch as right heart failure is absent. Peripheral arterial vasoconstriction was, as in normal subjects, demonstrated by a decrease in the renal blood flow. The finding of a concomitant fall in pulmonary blood volume and right atrial pressure indicates that the peripheral venous constriction is not extensive enough to prevent fully a shift of the blood volume. On the other hand, in the one patient in whom the pulmonary blood volume did not increase, the right atrial pressure was also maintained.

In Patient No. 387 with marked congestive heart failure, tilting did not produce any change in cardiac output or heart rate, although the right atrial pressure

sures, and renal clearances in 7 patients with mitral valvular disease without right heart failure

Stroke output (ml.)		*RA mean*		*PCV mean*		*PA mean*	
crh	*rhf*	*crh*	*rhf*	*crh*	*rhf*	*crh*	*rhf*
7	9	5	7	7	8	7	9
−15.3	−11.8	−2.2	−2.3	−4.6	−5.5	−3.9	−4.2
12.0	12.5	2.59	2.56	4.39	4.84	6.54	6.34
4.51	4.17	1.16	0.97	1.66	1.71	2.47	2.11
3.39	2.83	1.90	2.37	2.77	3.22	1.58	1.99
0.02–0.01	0.05–0.02	0.2–0.1	0.1–0.05	0.05–0.02	0.02–0.01	0.2–0.1	0.1–0.05

CPV/TBC (%)		*PAH (ml./min.)*		*Inulin (ml./min.)*		*Na^+ urinary excretion (mEq./L.)*	
crh	*rhf*	*crh*	*rhf*	*crh*	*rhf*	*crh*	*rhf*
6	7	5	7	5	7	5	6
−1.17	−1.76	−54.0	−36.6	−17.8	−13.6	−39.4	−37.8
4.04	4.01	29.2	39.3	10.4	11.7	41.9	37.7
1.65	1.51	13.0	14.8	4.64	4.42	18.7	15.4
0.71	1.17	4.15	2.47	3.84	3.08	2.11	2.45
0.6–0.5	0.4–0.3	0.02–0.01	0.05	0.02–0.01	0.05–0.02	0.2–0.1	0.1–0.05

decreased somewhat. This finding could be due to the presence of sustained increase in venomotor tone which prevents the shift of blood to the lower part of the body. This concept is supported by the findings of Burch[28] and Wood, Litter and Wilkins,[29] who demonstrated that the volume of blood contained in the peripheral system was less in patients with congestive heart failure than in individuals with a competent right heart function, indicating increased venoconstriction in the former. Thus, in right heart failure, regulatory mechanisms for maintaining the venous return are already operating in the recumbent position and counteract the pooling of blood in the upright position. Similarly, in studies on the effect of positive pressure breathing, high mask pressure did not decrease the cardiac output in patients with congestive failure, in contrast to the findings in normal individuals in whom the decrease in right heart filling pressure caused a decrease in the blood flow.[25]

Cardus, McKinnon and Wade[27] made an investigation similar to the present one, studying the circulatory effects of changing position in patients with mitral disease. Several important differences become apparent between these two studies, both in regard to technique and results. They tilted the patient to 40 degrees from the horizontal and found fewer alterations than we did. In their study, both pulse rate and systemic blood pressure were virtually unchanged. In our studies the pulse rate showed variable changes, but usually increased, except in those in right heart failure. The reaction of the pulse is of special importance in patients with mitral disease, since marked increase in pulse rate shortens the diastolic filling time to an extent necessitating a greater pressure head over the mitral valve to keep up the filling of the left ventricle. This can be seen in Patient No. 597, in whom the pulse rate increased from 85 to 118 per minute and the wedged pressure was unchanged although the cardiac output decreased.

Another important difference is the more advanced stage of disease in the patients of Cardus and associates,[27] with initially lower blood flow—in this respect they are more nearly comparable to the patients in failure, in whom no changes in blood flow were found in the present study as well.

The factor which gives rise to circulatory changes as the upright position is taken must be the diminished return to the right heart and the diminished pulmonary blood volume. The increase in heart rate and the decrease in systemic pulse pressure, with increased mean pressure, are the immediate regulatory steps taken to insure enough cerebral blood flow. The absence of those regulatory measure may be due: (1) to an insufficient stimulus, (2) to the presence of congestive failure, with less change in the venous return on changing position, or (3) to the modifying influence of, for example, digitalis glycosides, which may keep the heart rate low, especially in patients with atrial fibrillation.

The diminished pulsations of both right atrial and pulmonary wedged pressures in the upright position, as was pointed out by Lagerlöf[6] and Cardus,[27] and associates, were also found in the present study. They probably reflect the decreased filling of the pulmonary vascular bed. As pointed out by Cardus and associates,[27] an enlarged V wave in the wedged pressure curve cannot be used as evidence for an incompetent mitral valve. Conversely, the variation in the size of the V wave with different filling of the pulmonary vascular bed suggests that a large V wave in, for example, patients with arterial hypertension reflects increased pulmonary blood volume rather than incompetence of the mitral valve.

The diminished renal blood flow, glomerular filtration rate, and excretion of sodium in the upright position were of the same magnitudes as those seen in normal individuals. This renal vasoconstriction is probably not a specific renal reaction but signifies a part of the general systemic vasoconstriction elicited by tilting and governed by aortic–sinus caroticus reflexes. The decrease in renal blood flow seems to be of great importance—best correlated to these changes was the stroke volume—similar to what has been found under other circumstances in patients with heart disease.[30] The patient who was tilted head down reacted with increased renal clearances and excretion of sodium, but the excretion of water changed little. Thus, this reaction cannot be elicited by the intrathoracic volume receptors as suggested by Gauer and Henry.[31]

It was obvious that the patients in this study, as in many others, had fewer respiratory difficulties in the upright position than in the horizontal. On the other hand, it is noteworthy than one patient with mitral stenosis could be tilted head down and kept in this position for 30 minutes without discomfort. The question whether the respiratory symptoms in the horizontal position depend upon the increased blood volume in the lungs or upon the increased capillary pressure with increased exudation cannot be answered, since both blood volume and pressures varied in the same direction. Probably both give rise to sensations that are of importance for the symptom of orthopnea.

Summary

1. Ten patients with mitral valvular disease were investigated in the recumbent and in the erect postures (tilted 60 degrees head up). The cardiac output, pulmonary and systemic pressures, cardiopulmonary and total blood volumes, and renal clearances of inulin and para-aminohippurate, as well as the excretion of sodium, were determined.

2. In 7 patients without symptoms and signs of right heart failure the cardiac and stroke outputs decreased, as well as the pulmonary capillary and the right atrial pressures. In 2 patients with clinical signs of right heart failure the cardiac and stroke outputs remained unaltered.

3. The pulmonary arterial pressure fell moderately when the patients took the erect posture. The pulmonary arterial and the systemic arterial pulse pressures were generally diminished.

4. The cardiopulmonary blood volume fell in 3 instances. This was reflected by a concomitant decrease in pulmonary capillary venous pressure.

5. The renal clearance of inulin and para-aminohippurate as well as the excretion of sodium generally decreased.

6. One patient was tilted 30 degrees head down. No symptoms appeared, and no major hemodynamic change was recorded.

7. The results are discussed in view of possible hemodynamic factors that may cause orthopnea in heart disease.

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Movements of the heart during the period between the onset of relaxation and the beginning of ventricular filling

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A preceding communication dealt with the sequence of the contractile process. The present report is concerned with relaxation. The subjects, animals, and methods used were the same in the two investigations and have been considered in some detail in the previous study.[1] In brief, the normal human cardiac movements as recorded from the epigastrium, the suprasternal notch, and from numerous precordial points were analyzed in relation to the electrocardiogram and the carotid pulse (as recorded indirectly by a glycerine capsule). These motions were then compared with differentiated pressure curves as obtained from the great vessels and cardiac chambers of open-chest dogs. On the basis of such indirect evidence a hypothesis of the sequence of relaxation has been evolved.

The general schema utilized in designated movements is similar to that employed in the previous publication. The periods before and after the carotid incisural notch are called RI and RII. The abbreviation of the specific structure considered to be possibly related to or responsible for the motion is placed in parentheses and is capitalized in the case of the larger movements. Thus, RI(S) refers to a large motion occurring before the incisura, and thought to be due to relaxation of the interventricular septum, whereas RII (pr) indicates a small movement occurring after the incisura and believed to be dependent on relaxation of the papillary muscles of the right ventricle.

In the interpretation of the precordial traces, the directional orientation of the "pickup" device is significant. Records from the right and left parasternal and from the left mid-clavicular lines were obtained with the instrument pointed posteriorly. In these records a downward deflection indicates posterior movement, and an upstroke signifies anterior motion. The orientation of the left axillary, suprasternal, and epigastric recordings was such that an upstroke signifies either anterior or leftward, either anterior or headward, and either anterior or footward motion in these respective regions.

Results

The observations are summarized in Fig. 1 and illustrated in the several other

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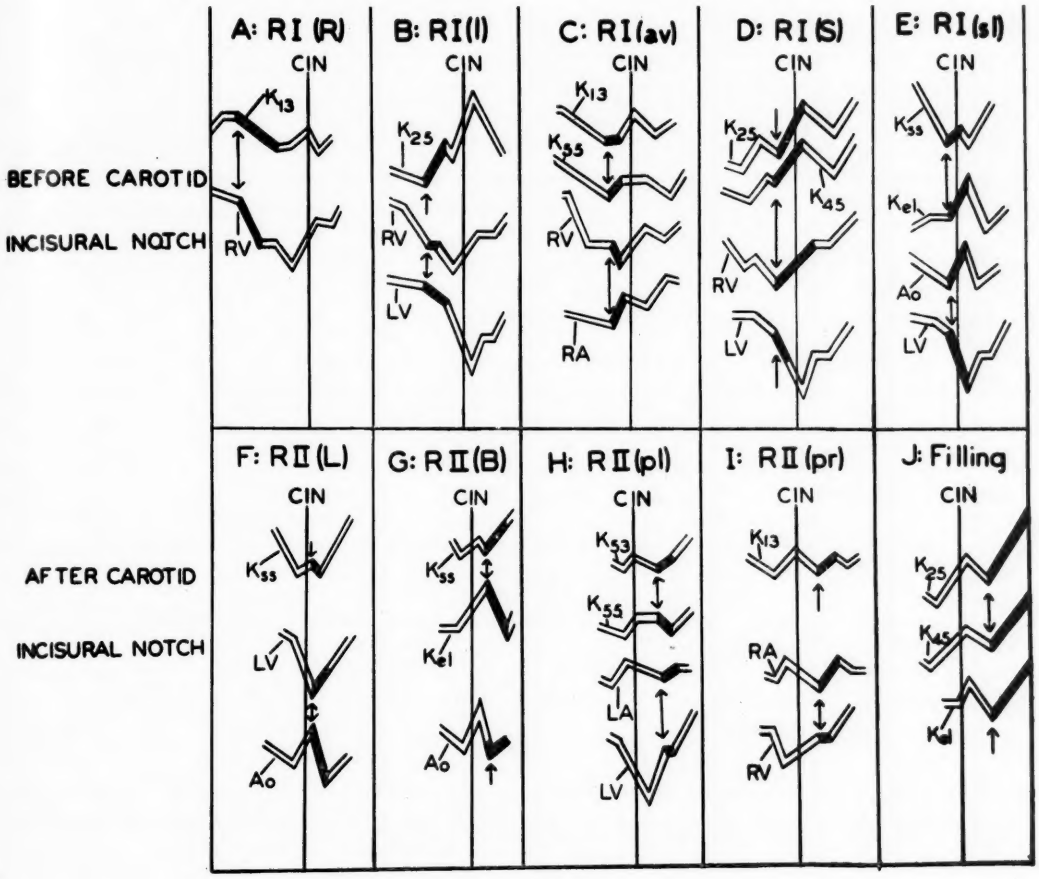

Fig. *1*. The diagram illustrates the motions observed between the onset of relaxation and the beginning of ventricular filling. The precordial movements (K) of the human subjects and the pressure velocity records from the aorta and from the cardiac chambers of the dogs are adjusted to a time scale corresponding to an identical duration of relaxation in the two species. The specific motions are designated by the arrows and by the black areas. *A*, The abrupt decline in the pressure velocity trace of the right ventricle (RV) indicates the onset of relaxation of this chamber. The corresponding inward motion in the upper right parasternal intercostal spaces (K_{13}) is possibly due to decreasing bulge of the tricuspid leaflets. *B*, The onset of sharp decline in the left ventricular velocity record associated with decreasing decline in the right ventricular derivative and with forward motion in the left parasternal (K_{25}) area is ascribed to release of the pull of the left ventricle on the interventricular septum. *C*, The rise in the right atrial velocity trace associated with decline in the right ventricular velocity record suggests that the tricuspid valve is moving toward the right atrium. This might be due to relaxation of papillary muscles but (see text) ascent of the tricuspid annulus is considered as the more likely cause. At the same time the records from human subjects show evidence (outward motion in both the right parasternal and left axillary areas) of increase in the transverse diameter of the heart. *D*, The large reciprocal motions in the two ventricular velocity traces point toward rightward movement of the interventricular septum. The counterpart in the human subjects is a large outward deflection in the left parasternal (K_{25}) and apical (K_{45}) regions. These several phenomena are ascribed to relaxation of the septum. *E*, The abrupt rise in the aortic derivative trace associated with increasing rate of decline in the left ventricular pressure is attributed to ascent of the aortic annulus. The simultaneous outward motion in the suprasternal (K_{ss}) and left epigastric (K_{el}) regions indicates vertical elongation of the heart. *F*, As the aortic velocity trace descends sharply, there is a rise (indicating a decreasing rate of fall in pressure) in the left ventricular velocity trace. These motions and the corresponding small decline in the suprasternal (K_{ss}) trace are attributed to downward bulge of the now closed aortic cusps. *G*, This second upstroke of the aortic and suprasternal traces is ascribed to relaxation of basilar fibers which, when contracted, exert a downward pull on the aortic annulus. The downstroke in the epigastric record indicates headward motion of the inferior border due to a change in shape of the ventricles as the semilunar rings ascend. *H* and *I*, The several observed phenomena are compatible with relaxation of the left (upstroke in the left atrial derivative and upper left axillary traces associated with downstrokes in the left ventricular derivative and lower left axillary records) and right (upstroke in the right atrial velocity and parasternal traces and downstroke in the right ventricular velocity record) papillary muscles. *J*, The large outward motion in the left precordial and epigastric regions indicate the beginning of passive ventricular filling.

Table I. *Summary of precordial movements during relaxation**

Designation (see text)		*RI(R)*	*RI(l)*	*RI(av)*	*RI(S)*
Description		↘ K_1	↗ K_2 and K_4	↗ K_1 or K_5	↗ Lower K_2 and K_4
Number of 10 subjects showing motion		8	9	K_1 8 K_5 8	10
Time after Q (sec.)	Range	0.27–0.33	0.29–0.37	0.30–0.41	0.33–0.42
	Average	0.294	0.328	0.357	0.377
Time relation to CIN (sec.)	Range	0.09–0.16 before	0.04–0.12 before	0.02–0.13 before	0.0–0.06 before
	Average	0.114 before	0.076 before	0.047 before	0.028 before
Usual size of motion		Moderate	Small	Small	Large
Possible mechanism		Onset of RV relaxation	Release of LV tug on IV septum	Release of pull on A-V rings	Relaxation of IV septum

*K_1: Right parasternal. K_2: Left parasternal. K_4: Left mid-clavicular. K_5: Left anterior axillary. K_{ss}: Suprasternal. KE: Epigastric.

figures. Those on the human subjects are indicated in Tables I and III and the findings in the dogs are presented in Table II.

I. Motions before the carotid incisural notch.

1. INWARD MOVEMENT IN THE RIGHT PARASTERNAL REGION. Eight of the 10 normal persons displayed a downward deflection beginning at approximately 0.29 second after the onset of excitation, or about 0.12 second before the carotid incisura. In some instances this was fused with the previous gradual downstroke in the same region, but in the majority of subjects this motion was distinct as a separate deflection (Figs. 1,*A* and 2,*A*). The movement, which is designated as RI(R), was largest in the upper intercostal spaces and decreased progressively in the lower regions. In patients with right ventricular hypertrophy it is markedly exaggerated in both the right and left parasternal regions,[2] and occurs later in relation to the carotid incisura.

The pressure velocity traces from the two ventricles of the dogs usually displayed a slow decrease during late systole. The initial sharp decline occurred first in the right ventricle in some animals (Fig. 3), but not in all of them (Table II).

Comment: These observations suggest that the changes observed in the normal persons and in some of the dogs were probably related to right ventricular activity, and represented the onset of relaxation in this chamber. Apparently, in the human subjects, the right ventricle usually started to relax first, but in the experimental animals it appeared that either chamber might precede the other.

The larger size of the downstroke in the upper intercostal spaces to the right of the sternum would suggest that in the normal human subjects the previous bulge of the tricuspid valves was diminishing as the pressure declined in the right ventricle. A descent of the right atrial floor would be expected to be more readily reflected in the right parasternal than in the left precordial region. However, consistent evidence of a decreasing bulge of the tricuspid valve was not found in the right atrial traces of the dogs.

RI(sl)	*RII(L)*	*Terminal relaxation movements*		
		RII(pl)	*RII(B)*	*RII(pr)*
↗ K_{ss} and KE	↘ K_{ss} ↗ KE	↗ Upper K_5 ↘ Lower K_5	↗ K_{ss} ↘ KE	↗ K_1
10	6	↗ Upper 7 ↘ Lower 7 Both 6	9	8
0.35–0.44	0.37–0.44	0.38–0.48	0.38–0.50	0.39–0.49
0.394	0.410	0.434	0.436	0.442
0.04 before 0.03 after	0.02 before 0.03 after	0.02–0.05 after	0.0–0.07 after	0.03–0.06 after
0.009 before	0.008 after	0.033 after	0.035 after	0.043 after
Large	Small	Small	Large	Small
First ascent of aortic ring; also descent of inferior border	Descent of aortic cusps	Relaxation of papillary muscles of LV	Second ascent of aortic ring; also ascent of inferior border	Relaxation of papillary muscles of RV

CIN: Carotid incisural notch. RV: Right ventricle. LV: Left ventricle. A-V: Atrioventricular. IV: Interventricular.

In the patients with right ventricular hypertrophy this inward motion is marked in the left as well as in the right parasternal region, whereas the normal subjects exhibited it mainly or entirely in the latter area. This finding indicates that some factor other than a bulge of the tricuspid valves is responsible for the movement in the presence of right ventricular hypertrophy. As has been indicated in a previous publication,[3] there is evidence for a large systolic rightward-forward motion of the heart in such subjects. Presumably, this is reversed as the right ventricle relaxes.

2. SMALL OUTWARD MOVEMENT IN THE LEFT PRECORDIAL AREA. Nine of the 10 normal persons exhibited an upstroke in the traces from the K_2 and K_4 regions, beginning about 0.03 second after the previous motion, or about 0.33 second after the start of excitation and 0.08 second before the carotid incisural notch (Figs. 1,*B* and 2,*B* and *C*).

Motions corresponding to this one were usually seen in the pressure velocity traces from the dogs (Table II). In most instances, increasingly steep decline of the left ventricular curve was associated with decreasing slope in the right chamber. An occasional animal displayed an actual upstroke in the right ventricular velocity trace as the record from the left side began its sharp decline (Fig. 3, *arrow 2*).

Comment: In the preceding publication, indirect evidence for the presence of an initial systolic backward tug (or forward push) on the interventricular septum by the left ventricle was presented. It would appear probable that the movement under discussion, which is designated as RI(l), represents the reverse of that motion. This motion was seen in most of the dogs, but in both species was smaller than the similar movement [RI(S)] which occurred a little later and which is ascribed to septal relaxation. If this reasoning is correct, it indicates that the mural fibers relax before those in the septal and subendocardial regions.

3. OUTWARD MOVEMENT IN THE RIGHT PARASTERNAL AND LEFT AXILLARY LINES. Eight of 10 persons exhibited a very small outward motion in the K_1 records (Figs. 1,*C* and 2,*A*, *second arrow*), and, likewise,

Table II. *Changes in pressure velocity as observed in dogs during ventricular relaxation**

Motion		*Onset sharp* ↘	*Increased LV* ↘ *Decreased RV* ↘	*RA and LA* ↗ *RV and LV* ↘
Number of dogs studied		14	14	12
Number showing motion		RV first 8 LV first 4 Simultaneous 2	10	RA 10 LA 2
Average time	After Q (sec.)	0.215	0.247	0.273
	Before or after AIN (sec.)	0.075 before	0.043 before	0.017 before
Probable mechanism		Start of ventricular relaxation	Release of LV pull on septum	Release of pull on A-V rings
Remarks		RV usually relaxes first	Reverse motion rarely seen	Effect masked in LA by decreasing bulge of mitral cusps(?)

*AIN: Aortic incisural notch. RA and LA: Right and left atria. RV and LV: Right and left ventricles. PA: Pulmonary artery.

8 of 10 displayed upward deflections in one or more of the K_5 traces (Fig. 4,*A* and *B*, *first arrow*). In some individuals there was simultaneous inward movement in the left anterior areas (Fig. 2,*B* and *C*, *second arrow*). These deflections occurred about 0.36 second after the beginning of excitation, and 0.05 second before the carotid incisural notch.

Most of the dogs exhibited a brief rise in the right atrial pressure velocity trace at approximately this time of the cycle (Fig. 3, *arrow 3*), and a few displayed a similar change in the left atrial record (Table II). The velocity traces in the two ventricles usually continued to decrease.

Comment: The data on the human subjects suggest that the transverse dimension of the heart is increasing at this time, whereas the data from the studies on dogs indicate rising atrial pressures. Such effects could be the result of the relaxation of those subepicardial fibers which, during contraction, pulled the rings of the atrioventricular valves toward the apex. Evidence that such a pull does occur has been presented by Rushmer,[4] and also in the preceding report.[1] This relaxation movement is designated as RI(av). The evidence, cited above, that the outer walls relax before the subendocardial regions makes it unlikely that it is due to release of the papillary muscles.

4. LARGE OUTWARD MOVEMENT OF THE LEFT PRECORDIUM. Approximately 0.38 second after the beginning of excitation, and 0.03 second before the carotid incisural notch, the largest precordial relaxation deflection was seen. This consisted of outward motion of the left anterior (K_2 and K_4) areas (Figs. 1,*D* and 2,*B* and *C*). This movement was apparently the reverse of the large inward deflection constantly found in the same region during the latter portion of isometric contraction. The aortic second sound occurred during this motion in each of 9 subjects.

Thirteen of the 14 dogs displayed reciprocal changes in the two ventricular traces; that on the right exhibited an upstroke (decreased velocity of pressure decline), with a simultaneous downstroke in the left ventricular record (Fig. 3, *arrow 4*).

Comment: In most normal persons this deflection is the largest seen during relaxation. The motion which apparently corresponds to it in dogs is usually the largest reciprocal movement in the ventricular velocity trace. In both species it is opposite in direction, and similar in magnitude, to those deflections during isometric contraction which have been ascribed to

RV ↗ *LV continued* ↘	*Aorta and PA* ↗ *LV and RV* ↘	*Aorta and PA* ↘ *LV and RV* ↗	*RA and LA* ↗ *RV and LV* ↘
14	12	12	12
13	Aorta and LV 11 PA and RV 10	Aorta and LV 12 PA and RV 8	RA 5 LA 1
0.276	Aorta 0.290 PA 0.305	Aorta 0.298 PA 0.310	——
0.014 before	Aorta 0 PA 0.015 after	Aorta 0.008 PA 0.020 after	——
Relaxation of septum	Release of pull on semilunar rings	Descent of semilunar cusps	Relaxation of papillary muscles
Motion usually large	Often biphasic (see text)	Reverse motion precedes and often follows	Effect on A-V cusps usually masked by decreasing bulge(?)

A-V: Atrioventricular.

contraction of the septum.[1] These several facts, and particularly the reciprocal changes in the ventricular pressures, constitute indirect evidence that these motions are related to relaxation of the interventricular septum, which is then displaced sharply toward the right ventricle because of the lower pressure in this chamber. This movement, which is designated RI(S), occurs at the time of the second heart sound in the aortic area. Possibly, the normal delay in the pulmonic, as compared to the aortic, second heart sound is somewhat related to the effect of septal displacement on the right ventricular pressure.

The apparent discrepancy between these findings and those of Rushmer,[4] who observed only minimal displacement of the interventricular septum, is probably not significant. The records in the dogs are related to the rate rather than the degree of decline in pressure, and it is probable that the magnitude of the precordial motions tends to reflect the abruptness rather than the extent of the cardiac movement.

5. OUTWARD MOVEMENT OF SUPRASTERNAL AND EPIGASTRIC REGIONS. About 0.39 second after the beginning of excitation, and 0.01 second before the carotid incisural notch, two motions were observed in all of the normal subjects. These were small upward deflections in the traces from the suprasternal notch (indicating headward movement of the aorta) and larger upstrokes in the records from the epigastrium (indicating footward motion of the inferior border of the heart) (Figs. 1,*E*, 2,*D* and *E*, and 4,*C* and *D*). Since in these regions the "pickup" device was pointed obliquely in footward and headward directions, respectively, this interpretation seems justified.

Movements which corresponded to these were observed in the dogs. At the same relative time in the cycle most of them displayed a sharp decline in the pressure velocity trace of the left ventricle, associated with a rise in the record obtained from the aorta (Fig. 5, *arrow 2*). Similar findings were usually observed about 0.01 second later in the right ventricle and pulmonary artery (Table II).

Comment: The observations on the animals, showing an increased rate of decline in pressure in the ventricles, associated with a momentary reversal of the previous decrease in the great vessels, are evidence that the semilunar rings are ascending. The motion is, therefore, designated RI(sl). In the human subjects the

Table III. *Summary of normal precordial movements during ventricular contraction and*

Motions during contraction				
Phase of contraction	*Motion*	*Average time after Q (sec.)*	*Designation of motion*	*Phase of relaxation*
Isometric I Before onset of first heart sound	↘ or ↗ K_2 to K_4	0.037	CI(l)	Early
	↘ Upper K_5 ↗ Lower K_5	±0.012	CI(pl)	Late
	↘ K_1		CI(pr)	Late
Isometric II First heart sound to start of RV ejection	↘ KE or lower K_2 to K_4 ↗ K_{ss} or upper K_2 or K_4	0.053	CII(L)	Late
	↗ K_1	0.055	CII(R)	Early
	↘ K_2 to K_4	0.068	CII(S)	Early
	↘ K_1 ↘ KE and K_{ss}	0.078	CII(av, sl)	Early
Isometric III RV ejection to LV ejection	↗ Lower K_2	0.088	CIII(rR)	—
	↘ K_{ss} ↗ KE	0.091	CIII(B)	Late
	↗ K_1 and K_2 ↘ K_5	0.094	CIII(s)	—

simultaneous descent of the inferior border of the heart and ascent of the aorta would suggest that the heart is elongating in its vertical dimension. Apparently, it represents relaxation of fibers which extend from the semilunar rings to the inferior margin of the heart.

II. Motions after carotid incisural notch.

1. INWARD MOVEMENT IN THE SUPRASTERNAL REGION. Six of the 10 subjects displayed a small downward motion in the suprasternal traces, occurring approximately 0.01 sec. after the carotid incisura (Figs. 1,*F* and 4,*C*). Outward motion in the epigastrium which had started slightly earlier continued, indicating that the inferior margin of the heart was still moving footward (Figs. 2,*D* and 4,*D*).

All of the dogs (Table II) exhibited a momentary decrease in the rate of decline of pressure in the left ventricle, associated with a more rapid decline in the aorta (Fig. 5, *arrow 3*). Corresponding changes were frequently but not always observed in the traces from the right ventricle and pulmonary artery.

Comment: These findings can be ascribed to downward movement of the semilunar cusps into the ventricles as the pressure in these chambers rapidly declined. The time and high frequency of these motions would make one suspect that they actually may represent heart-sound vibrations. However, demonstration (Fig. 5) that the frequency is less than that of the sounds, and that the aortic and left ven-

relaxation

Reverse motion during relaxation			*Remarks and interpretation: Contraction and relaxation of*
Motion	*Average time relative to CIN (sec.)*	*Designation of motion*	
↗ K_2 to K_4	0.076 before	RI(l)	Left ventricle causing pull (↘) or push (↗) on septum
↗ Upper K_5 ↘ Lower K_5	0.033 after	RII(pl)	Papillary muscles: often masked by larger succeeding or preceding motions
↗ K_1	0.043 after	RII(pr)	
↘ K_{ss} ↗ KE	0.008 after	RII(L)	Lower left ventricle; headward displacement of blood; mitral closure. Bulge of aortic cusps
↘ K_1	0.114 before	RI(R)	Right ventricle; closure and bulge of tricuspid leaflets
↗ K_2 to K_4	0.028 before	RI(S)	Septum: largest motion during contraction and relaxation
↗ K_1 and K_5	0.047 before	RI(av)	Descent av rings } Subepicardial fibers (?)
↗ K_{ss} and KE	0.009 before	RI(sl)	Descent sl rings } Subepicardial fibers (?)
——	——	——	Recoil of right ventricle
↗ K_{ss} ↘ KE	0.035 after	RII(B)	Pull by muscles at base on semilunar rings
——	——	——	Displacement of septum to right by high LV pressure

tricular traces always display reciprocal motions, makes this assumption improbable.

This motion is called RII(L) in Tables I and III, because it seems to be mainly due to relaxation of the left ventricle. It appears to represent a continuation of the process which causes the previous movement. Thus, as the fibers which pass from the semilunar rings to the inferior margin begin to relax, there is elongation with ascent of the semilunar rings. However, as the inferior border continues to descend, the rapid decline in ventricular pressure allows the now closed semilunar valves to move sharply downward. This, in turn, causes a momentary decrease in the rate of decline in pressure in the ventricles.

2. TERMINAL MOVEMENTS OF RELAXATION. The largest and most frequently found final motions in the human subjects consisted of a sharp downstroke in the epigastrium (Figs. 1,*G*, 2,*D*, and 4,*D*) accompanied by a large outward deflection in the suprasternal traces (Figs. 2,*E* and 4,*C*). At approximately the same time, most of the right parasternal records exhibited outward motion (Fig. 2,*A*). In some subjects, small respective outward and inward deflections were observed in the upper and lower intercostal spaces in the left anterior axillary line (Fig. 4,*A* and *B*).

The corresponding movements were sometimes, but not always, seen in dogs. A large upstroke in the aortic velocity records was frequently observed (Fig. 5,

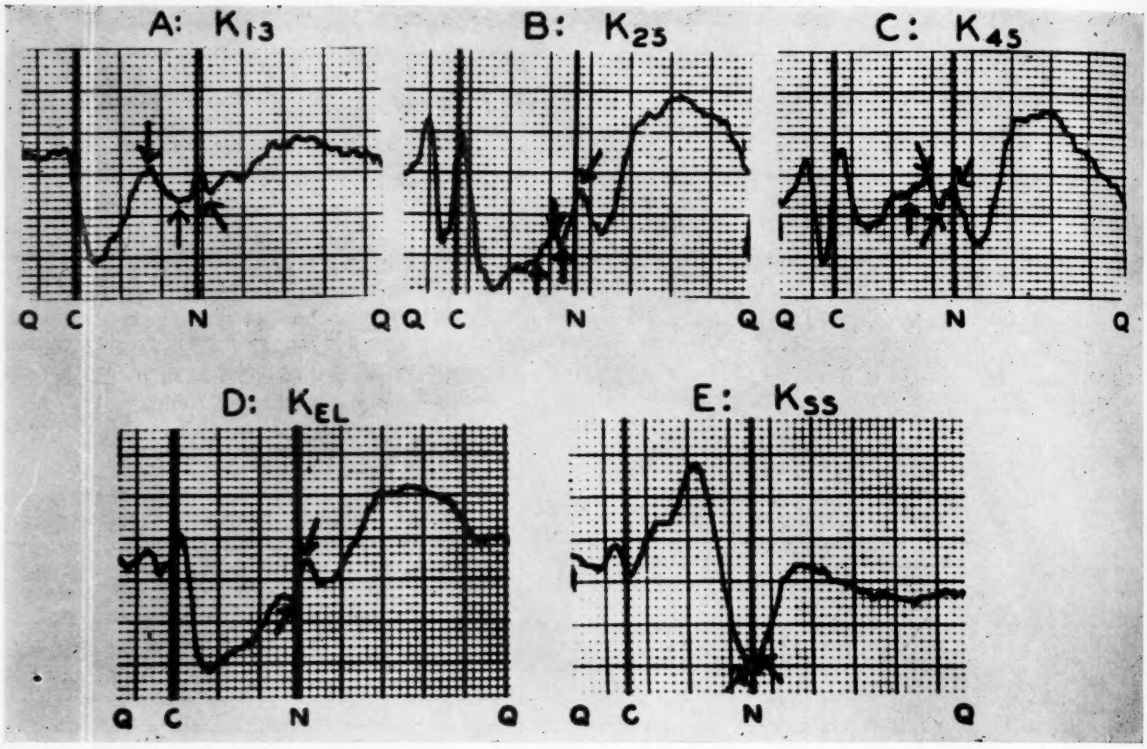

Fig. *2*. Precordial motions during relaxation, in D.G., a normal 26-year-old man. Paper speed 50 mm./sec. All traces start and end at onset of ventricular excitation. *C*, Carotid upstroke; *N*, carotid incisural notch. *A*, The first arrow designates the downstroke ascribed to right ventricular relaxation [RI(R)]. The second indicates the very small upstroke attributed to rightward motion of the tricuspid annulus [RI(av)]. The third arrow points to the larger upstroke which is thought to represent relaxation of the papillary muscles of the right ventricles [RII_4(pr)]. The motions between the second and third arrows apparently are related to relaxation of the interventricular septum (upstroke) and the change in shape as the aortic annulus ascends (downstroke). These two motions are larger at other areas (*B* and *C*). *B* and *C*, These records from the fifth intercostal space in the left parasternal and mid-clavicular lines are similar. Each shows two outward motions, first and third arrows, at 0.09 and 0.03 sec. before the incisural notch (*N*). These are, respectively, attributed to release of the backward pull of the left ventricle [RI(l)] and relaxation of the interventricular septum [RI(S)]. The small downstroke indicated by the second arrow is ascribed to a change in shape as the rings of the A-V valves ascend [RI(av)]. The later and larger downstroke, fourth arrow, corresponds to the large upstroke in the suprasternal notch (*E*) as the aortic annulus ascends [RII(B)]. *D* and *E*, Two motions are shown. The first, which starts just before the incisura, indicates vertical elongation of the heart [RI(sl)] as shown (*first arrow*) by outward deflection of the traces from the epigastrium (*D*) and from the suprasternal notch (*E*). Immediately after the incisura the ascent of the suprasternal records becomes steeper (*E, second arrow*), and the inferior border (*D, second arrow*) and the left precordial traces (*B* and *C, fourth arrow*) move inward. These several findings are ascribed to release of footward pull on the aortic annulus by basal fibers, with a change in shape of the left ventricular cavity [RII(B)].

arrow 4), but in some animals was confused with the similar movement starting earlier. The right and left atrial traces occasionally displayed an upstroke at this time (Fig. 3, *arrow 5*).

Comment: The simultaneous occurrence of a large headward motion in both the suprasternal and the epigastric regions can be explained as follows: The former movement, appearing at a time when ejection has ceased and when runoff from the aorta would necessarily have the opposite effect, can only be ascribed to ascent of the aortic ring. The downstroke in the epigastric records indicates a change in shape of the ventricles; the inferior border moves headward as the aortic valves rise. These findings suggest relaxation of basilar fibers which pull the annulus downward but do not extend to the inferior border. Since the deep bulbospiral muscle is made up of such fibers, it seems possible that the motions in question are related to relaxation of this structure.

This large movement is designated as RII(B) because it is ascribed to the fibers

at the base of the left ventricle. It should be noted that this second release of the aortic annulus differs from the one previously described [RI(sl)], which is associated with footward rather than headward motion of the inferior border and is attributed to muscles which cause systolic shortening of the vertical dimension.

The other, smaller and less constant, terminal motions are believed possibly to be related to relaxation of papillary muscles. They are opposite in direction to the initial deflections ascribed to contraction of these muscles.[1] Some of the dogs exhibited upstrokes in the atrial pressure velocity traces at a corresponding time in the cycle. The inconstancy of these motions in both species was probably related not only to their small magnitude but also to the effect of the declining ventricular pressure. This would tend to allow the atrioventricular cusps to sag downward, whereas release of the papillary muscles would have the opposite effect. These two inconstant motions are designated as RII(pl) and RII(pr).

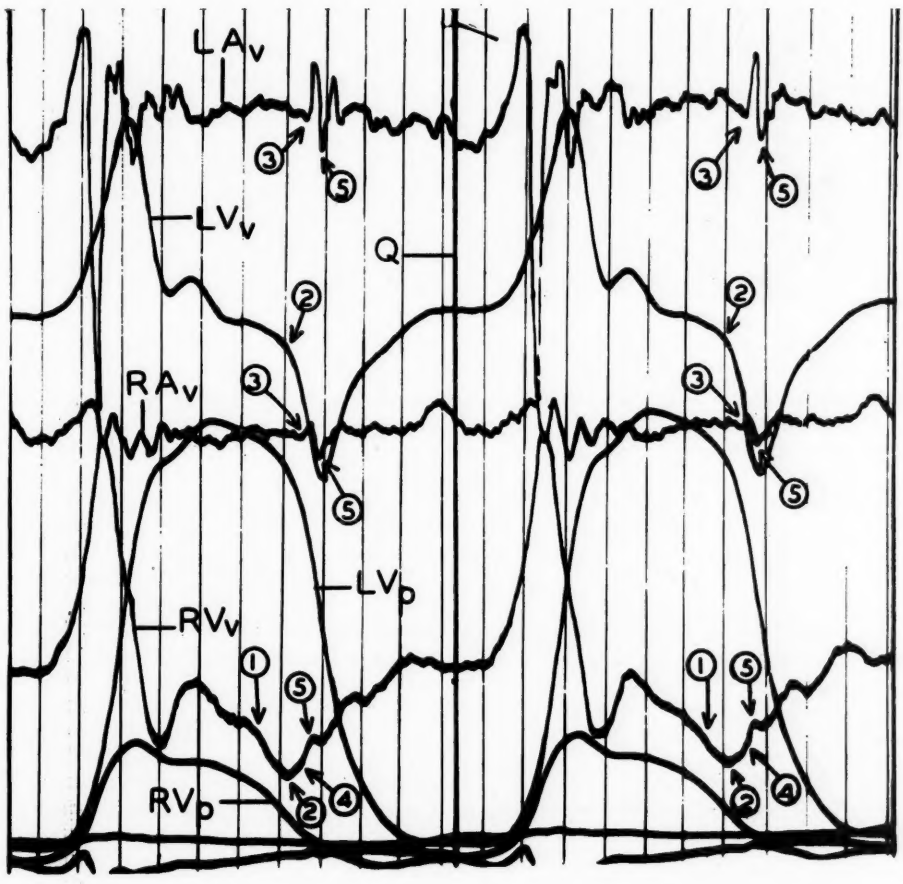

Fig. 3. Atrial and ventricular pressure velocities during relaxation. Time lines 0.04 sec. The pressure, *p*, and the pressure velocity, *v*, curves from the four cardiac chambers are shown during two successive cycles, starting and ending with the onset of ventricular excitation. The right ventricular velocity curve shows the first sharp downstroke (*1*), indicating the onset of relaxation [RI(R)]. As left ventricular relaxation starts (*2*), there is a small upstroke, indicating a decreased rate of fall in pressure in the curve from the right ventricle (*2*). This soon becomes more abrupt (*4*). These respective declines in the rate of drop in pressure in the right ventricle are thought to be due to release of the left ventricular pull on the septum (*2*) and relaxation of the septum (*4*). In the text, these motions are designated as RI(l) and RI(S). Each atrial velocity trace shows two abrupt upstrokes. The first of these (*3*) is ascribed to release of the downward pull on the atrioventricular rings [RI(av)], and the second (*5*), which is associated with a downstroke in the right ventricular trace is attributed to relaxation of the papillary muscles [RII(pl) and RII(pr)].

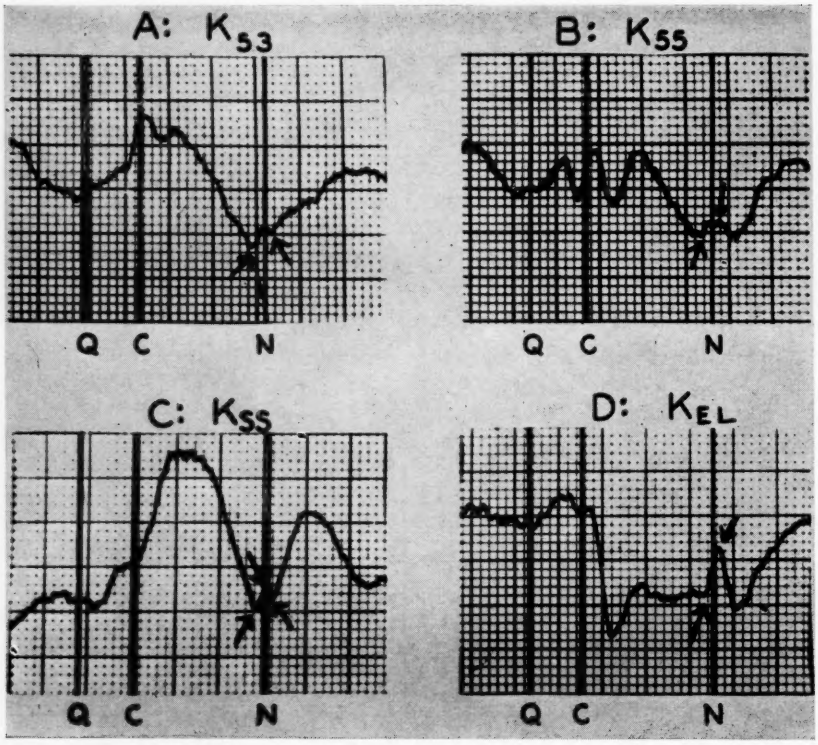

Fig. 4. Left axillary, suprasternal, and epigastric movements during relaxation. Paper speed 50 mm./sec. Records start and end at onset of P wave of ECG. *Q*, Onset of QRS; *C*, carotid upstroke; *N*, carotid incisural notch. *A* and *B*, Both records display a small upstroke (*first arrow*) about 0.02 second before the carotid incisural notch. This deflection, designated as RI(av) in the text, is thought to be due to increase in transverse diameter as the systolic pull on the rings of the atrioventricular valves is released (see Fig. 2,*A*; *second arrow*). At 0.02 second after the incisural notch the K_{53} record (third intercostal space, anterior axillary line) exhibits an upstroke, whereas the trace taken two intercostal spaces below (*B*) shows a downstroke (*second arrow*). These motions are called RII(pl), and are thought to be related to relaxation of the papillary muscles of the left ventricle. They are not seen in all persons. *C* and *D*, The trace from the suprasternal notch (*C*) exhibits two upstrokes separated by a smaller downstroke, whereas that from the epigastrium (*D*) displays a large outward deflection followed by inward motion, indicating footward and then headward movement of the inferior border of the heart. The initial upstroke in both traces is ascribed to relaxation of muscles which extend downward from the aortic annulus to the inferior margin of the heart. The first effect of relaxation RI(sl) of these fibers is to allow vertical elongation. However, because the pressure in the left ventricle is falling rapidly, the now closed aortic cusps descend toward the ventricle, producing the downstroke in the suprasternal trace *C*, *second arrow* [RII(L)]. About 0.02 second after the incisura the muscles at the base of the left ventricle appear to relax [RII(B)], allowing a second and sharper ascent of the suprasternal trace. At the same time, change in the shape of the ventricle allows the inferior border to ascend (*D*, *second arrow*). Note the similarity between *C* and the aortic velocity trace in Fig. 5.

Discussion

An attempt to integrate the events during contraction with those of relaxation is illustrated in Table III. Inspection of this table not only confirms the statement of Fracastorius as quoted by William Harvey,[5] concerning the complexity of cardiac motion, but also reveals certain gaps in the tentative conclusions.

The interpretation of the sequence of events as presented is somewhat arbitrary and is based on the mean times in different persons and in different dogs. Despite general broad agreement some differences

were observed. Thus, in the dogs, relaxation sometimes seemed to begin on the left side, whereas in human beings the data suggested that the right ventricle initiated the process. Similarly, the terminal movements ascribed to relaxation of papillary muscles, although inconstant in both species, were encountered less frequently in the dogs. Despite the occasional disagreement the correspondence appeared to be surprisingly good when it is remembered that two different species were stud-

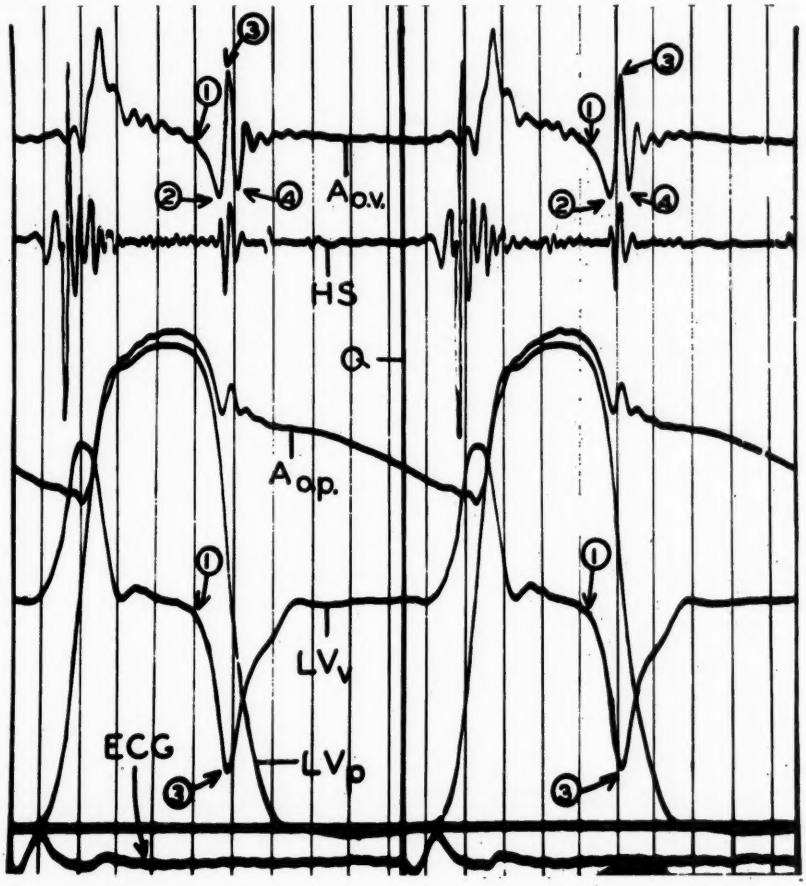

Fig. 5. Left ventricular and aortic pressure velocity during relaxation. Time lines 0.04 sec. The curves of pressure, *p*, and pressure velocity, *v*, in the left ventricle and in the aorta are shown during two successive cycles, starting and ending at Q. The heart sounds (*HS*), as recorded directly from the left ventricular wall, and the ECG are also shown. The onset of the left ventricular relaxation (*1*) is shown by a sharp decline in the pressure velocity trace from this chamber and in that from the aorta. While the ventricular drop is still rapid, an upstroke in the aortic trace (*2*) occurs at the time of the incisura and of the second heart sound. This motion, which is designated as RI(sl) in the text, is ascribed to the first ascent of the aortic annulus. About 0.01 sec. after the incisura the aortic velocity trace exhibited an abrupt downstroke (*3*), and at the same time the ventricular record displayed an upstroke, indicating a decreased rate of decline in pressure. This movement is called RII(L) and is attributed to a sudden descent of the closed aortic cusps into the left ventricle. The last motion (*4*) is characterized by a rise in the aortic velocity curve. This is thought to be due to a second ascent of the aortic annulus as the muscles at the base of the left ventricle relax [RII(B)]. A reciprocal downstroke in the ventricular trace was seen in some of the dogs, but not in this one. The much higher frequency of the second heart sound and the presence of similar small deflections in the aortic pressure trace make it improbable that the deflections in the aortic velocity trace represent heart-sound vibrations. Note the similarity of the aortic curve to that of the human record from the suprasternal notch in Fig. 4,*C*.

ied, that anesthesia was used and the chest cavity was opened in the animals, and that interpretations of the velocity of change in pressure in adjacent areas of the dogs were compared with concepts derived from studies of movements of the chest wall in normal human subjects.

An ideal summary of the ventricular events would entail knowledge not only of their sequence but also of the specific muscle bundles responsible for each movement. This has been achieved only by inference, and the interpretations in Table III are based on assumptions from indirect evidence. Furthermore, it is as yet not possible to achieve a clear integration between the observed motions and the mechanical problem of the points of fixation in a bewildering syncytium of muscle fibers.

The data are in general accord with those of Rushmer,[4] who utilized more direct techniques. Our findings support his concepts of the importance of the motions of the valve rings toward and away from the apex during contraction and relaxation, respectively.

The left ventricular outflow tract is encircled by the thick, deep bulbospiral muscle.[6] The observations on both dog and man suggest that this muscle is one of the last to contract and to relax. The mechanical advantage of such a sequence would seem obvious. Early contraction of this relatively powerful muscle would impair ejection by causing functional stenosis. There is evidence that this sometimes occurs and produces a systolic murmur and a gradient between left ventricular and aortic pressures,[7] without actual structural disease of the aortic valve. It is possible that a similar mechanism in the right ventricular outflow tract is responsible for the common functional ejection murmur at the pulmonary area of healthy young persons. Late relaxation of these basilar muscles probably has the advantage of lending support for the semilunar valves during the period immediately after closure, when the pressure in the great vessels is still relatively high.[8]

The findings in Table III suggest that the respective sequences of contraction and of relaxation are as follows: Contraction appears to proceed from the papillary and subendocardial muscles to the inferior wall of the left ventricle, thence to the free wall of the right ventricle, then to the septum, and, finally, to the free wall and the base of the left ventricle. The relaxation sequence seems to involve successively the right ventricular wall, the outer layers of the left ventricle, the septum, the inferior margin, and, finally, the subendocardial and papillary muscles on both sides and the base of the left ventricle. The idea that the duration of the relaxation of the thin right ventricle is longer than that of the thicker left is surprising and calls for confirmation by more direct techniques.

Although there is still some uncertainty as to the finer details of the depolarization and repolarization processes, the evidence published by numerous investigators indicates a general correspondence between these electrical phenomena and the mechanical sequence as here listed.

The data suggest that contraction spreads from subendocardial to subepicardial areas and from apex to base. Relaxation apparently proceeds from outside to inside, but from apex to base. Thus, the "mechanical vector" of relaxation would, like the repolarization vector, appear to be somewhat but not exactly opposite to the vectors of early systole. The data, therefore, suggest that there is a mechanical as well as an electrical ventricular gradient and that the two tend to be parallel. If this concept is correct, it follows that the electromechanical lag is of somewhat similar duration in the various portions of the ventricular muscle.

The subjects studied were deliberately chosen to represent a fairly wide age group —19 to 59. Significant age differences in the qualitative spread of contraction and of relaxation were not noted. It did appear that some motions were of larger size in the young persons, and that the reverse was true of other movements. However, a larger group of subjects representing an even broader age span should be studied before an opinion is justifiable.

Finally, it should be emphasized that the conclusions here drawn, concerning cardiac motions, are based on indirect methods. The degree of agreement noted by the two entirely different techniques

points toward a general validity of the ideas. However, attempts are in progress to develop more direct techniques, in order to subject the tentative concepts to more definitive investigation.

Summary

The sequence of ventricular relaxation, as studied by indirect methods, appears to be as follows.

A. Before the carotid incisural notch. (1) In some dogs and in most normal human subjects the process seems to begin in the right ventricle. (2) The onset of left ventricular relaxation is apparently associated with a small forward motion of the left precordial region. (3) As the fibers exerting a pull on the atrioventricular rings relax, the transverse diameter of the heart increases and the atrial pressures tend to rise. (4) A large forward motion of the precordium starting just before the second heart sound is probably due to relaxation, with rightward displacement of the interventricular septum. At a similar time there is respective increase and decrease in the rate of fall in pressure in the left and right ventricles of dogs. (5) A sharp upstroke in the aortic pressure velocity curves of dogs occurs while the pressure in the left ventricle is declining rapidly. At the corresponding time the curves in human beings display evidence of vertical elongation of the heart. These several movements are attributed to relaxation of fibers which reach from the rings of the semilunar valves to the inferior cardiac border.

B. After the carotid incisural notch. (1) Soon after the preceding motion there is a descent of the closed semilunar cusps. This is shown in dogs by a decrease in the rate of fall in pressure in the ventricles, associated with a downstroke of the aortic curves. In some of the records from human subjects there is a corresponding brief downstroke in the traces from the suprasternal notch. (2) The last major movement of relaxation is indicated in the dogs by a second rise in the aortic pressure velocity curve. A corresponding sharp upstroke in the suprasternal records from human subjects occurs and is regularly accompanied by a decline in the epigastric traces. This motion points toward a change in shape of the ventricular cavities as release of the basilar muscles allows a second headward rebound of the semilunar rings. It is possibly related to relaxation of the deep bulbospiral muscle. (3) Small inconstant terminal motions are thought to be the results of relaxation of papillary muscles. These movements are often masked by the opposite effects of the declining ventricular pressure, with decreasing bulge of the atrioventricular cusps.

These several motions are analogous with and opposite to those observed during isometric contraction. The processes of contraction and of relaxation appear to follow sequences closely resembling those of excitation and of repolarization.

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The systemic and coronary hemodynamic effects of guanethidine*

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Although there are some reports concerning the pharmacologic action of guanethidine ([2(octahydro-1-azocinyl) ethyl] guanidine sulfate, Ciba 5864-SU),[1-3] it seemed that additional information might be derived from a study in a larger number of animals, particularly for the clarification of the action of guanethidine in acute intravenous dosage to the intact animal. Therefore the following study was made.

Material and methods

The present hemodynamic study was divided into two parts, in the first of which were 13 mongrel dogs which weighed between 15 and 28 kilograms and averaged 21.9 kilograms. Anesthesia was secured by subcutaneous administration of 3 mg. of morphine sulfate per kilogram of body weight, followed in 1 hour by 0.25 ml. per kilogram of a 50/50 mixture of Dial-urethane and veterinary pentobarbital.† During the ensuing 1 hour after the administration of the intravenous anesthetic, cardiac catheters were manipulated fluoroscopically into the pulmonary artery, coronary sinus, and right atrium, and a Cournand needle was placed percutaneously into the femoral artery. One hour after the anesthetic was given, cardiac output was determined by the Fick principle. Expired air was collected for a total of 5 minutes in a Tissot spirometer, and coronary blood flow was determined by the nitrous-oxide saturation method. Central venous pressure was measured by the cardiac catheter with its tip in the right atrium, whereas pulmonary arterial and systemic arterial pressures were measured, respectively, through the cardiac catheter in the pulmonary artery and the needle in the femoral artery. All pressures were recorded with Statham strain gauges and recorded on the Gilson macropolygraph.

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†Dial-urethane was furnished through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J., and contains 100 mg. of Dial per milliliter, 400 mg. of monoethylurea per milliliter, and 400 mg. of urethane per milliliter. Veterinary pentobarbital contains 60 mg. of pentobarbital per milliliter.

The mean pressure was determined by electrical integration of the pressure curve. Cardiac rate was determined from an appropriate electrocardiographic lead. Blood-oxygen and carbon-dioxide contents were determined by the Van Slyke-Neill method, whereas nitrous-oxide analyses were done by the method of Orcutt and Waters. Oxygen and carbon-dioxide content of the expired air were determined by the method of Scholander. Whole blood pH was determined with a Cambridge Model R pH meter. The formulas for calculations are those generally used.[4] Work was calculated by the Starling formula of mean arterial blood pressure times cardiac output, using appropriate constants and not subtracting the right or left atrial pressure. The guanethidine was given as a single dose of 15 mg. per kilogram of body weight intravenously through the right atrial or pulmonary arterial catheter. After waiting periods which averaged 22 minutes, determinations of cardiac output and coronary blood flow were repeated.

In the second part of the study the response of blood pressure in the femoral artery, pulmonary artery, and right atrium was observed when the administration of guanethidine was preceded or followed by 5 mg. of phentolamine. Since it is known that the administration of reserpine produces catecholamine depletion,[5,6] further studies were made in a group of animals to which reserpine had been administered in a dose of 0.1 to 0.2 mg. per kilogram intramuscularly for 48 hours prior to the acute administration of guanethidine in a dose of 10 to 15 mg. per kilogram intravenously. In the first of this group, only the response of pressure to guanethidine was measured, but in the latter group of 6 dogs, cardiac output was measured as well by the Fick principle, before and after guanethidine. The details of the latter study were similar to those of the first portion of the study except that coronary blood flow was not determined, and in some cases the animals were sufficiently depressed by reserpine so that the anesthetic dose was reduced.

Results

Results are summarized in the Tables I, II, and III.

Within a few seconds after administration of guanethidine there was a decrease in systemic arterial pressure, accompanied, generally, by a transient rise in pulmonary arterial pressure and a decrease in right atrial pressure. Over the next minute or so the arterial pressure tended to rise again, becoming considerably elevated above the control value and accompanied by an increase in heart rate. The pulmonary arterial pressure continued to remain elevated, and the right atrial pressure rose slowly, remaining at a higher level than it had been prior to the administration of the drug. Although the arterial pressure tended to fall slowly after the initial peak, the decline was sufficiently gradual so that the mean pressure was still considerably elevated during the time of the second determination of cardiac output and coronary blood flow, an average of 22 minutes after the administration of the drug. At the time of the second study the heart rate was increased by 43.0 per cent ($p < 0.001$), the mean systemic arterial blood pressure was elevated 15.1 per cent ($p < 0.001$), and the mean pulmonary arterial pressure was 42.9 per cent higher ($p < 0.001$). Whereas right atrial pressure at the time of the second study had fallen somewhat toward the control level, the mean was still variably, but not significantly, elevated (+ 21.9 per cent, $p < 0.1$). The minute volume of respiration did not change significantly. However, the oxygen consumption was increased 21.7 per cent ($p < 0.001$) and carbon-dioxide excretion was similarly elevated (20.4 per cent, $p < 0.001$), with the body respiratory quotient unchanged. The arterial hemoglobin increased 18.8 per cent ($p < 0.001$) and the hematocrit was 22.7 per cent more ($p < 0.001$), whereas the femoral arterial pH (−0.06 units, $p < 0.001$) and coronary sinus pH (−0.04 units, $p < 0.01$) decreased slightly but consistently. As would be expected with the increase in hematocrit and hemoglobin, the arterial and mixed venous oxygen content both increased significantly (11.9 and 22.6 per cent, respectively). The arteriovenous oxygen difference was significantly decreased (−20.9 per cent, $p < 0.05$). Arterial and mixed venous carbon-dioxide content fell significantly, and the arterio-

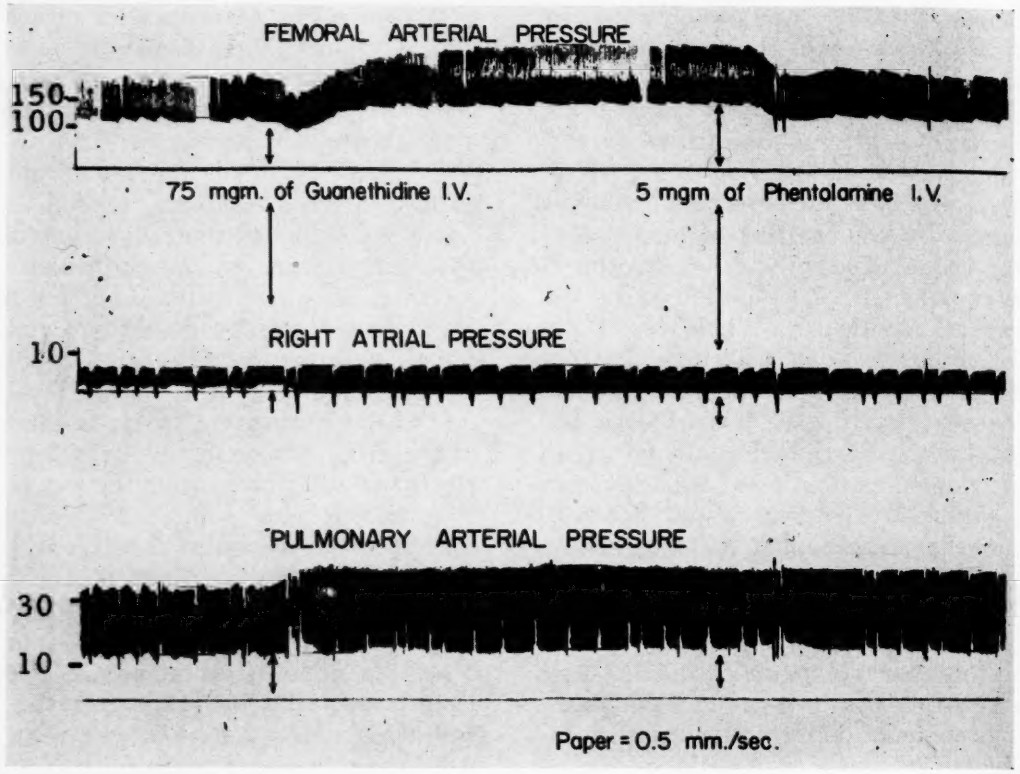

Fig. *1*. The typical response of pressure to an intravenous dose of guanethidine is shown and the change in the response which followed intravenous administration of phentolamine.

venous carbon-dioxide difference was significantly decreased. The coronary sinus carbon-dioxide content decreased significantly (−5.1 per cent, $p < 0.01$), with the arterial–coronary sinus carbon-dioxide difference unchanged. The slight decrease in cardiac respiratory quotient was not significant.

Cardiac output increased 71.4 per cent ($p < 0.02$). The increase was quite variable from animal to animal, however, ranging from a decrease of 0.7 liter per minute in one animal to an increase to 8.1 liters per minute in another, and with essentially no change in a few others. Similarly, total peripheral resistance was variable, increasing or decreasing considerably in certain cases. The over-all average of peripheral resistance decreased (26.6 per cent, $p < 0.02$), but total pulmonary resistance did not change significantly. Left ventricular work was variably but significantly increased (+106.8 per cent, $p < 0.01$), as was right ventricular work (+161.5 per cent, $p < 0.01$). Coronary blood flow increased variably (+0 to +268 per cent) but significantly ($p < 0.01$). Left ventricular oxygen consumption increased by 82.5 per cent ($p < 0.001$), and coronary vascular resistance decreased 26.7 per cent ($p < 0.01$). The index of efficiency, which relates left ventricular oxygen consumption per 100 grams per minute to left ventricular work, did not change significantly.

Phentolamine administered to the anesthetized animals immediately prior to administration of guanethidine was found to prevent the usual rise in arterial pressure. If phentolamine was administered subsequent to the guanethidine when the arterial pressure was already elevated, the pressure quickly fell to the control "pre-guanethidine" level, as shown in Fig. 1. Fig. 2 reveals the fact that pretreatment with reserpine, 0.1 to 0.2 mg./Kg./day for 2 days, prevented the increase in arterial pressure which ordinarily occurs after administration of guanethidine, and Table III reveals the general hemodynamic effects of guanethidine in 6 dogs pretreated with reserpine. Mean heart rate increased while systemic mean arterial blood pressure decreased, and pulmonary arterial and right

atrial pressures rose. In contrast to the untreated dogs, those pretreated with reserpine did not increase their oxygen consumption, or carbon-dioxide liberation after being given guanethidine, and their cardiac output varied, without a significant trend in either direction. Total peripheral resistance decreased in 5 of 6 dogs, whereas total pulmonary resistance rose in 3 and fell in 3. A rise in hemoglobin, and arterial and mixed venous blood oxygen content per 100 ml. of blood, as well as an increase in hematocrit, occurred consistently after administration of guanethidine in these animals which were pretreated with reserpine.

Discussion

Clinical trials have indicated that a considerable hypotensive response may be elicited in man by guanethidine.[3,7,8] The hypotension has been accentuated by the orthostatic position. Acute intravenous administration is reported to cause a transient hypertensive phase before the prolonged hypotensive phase ensues[9]; indeed, the hypertensive response may be alarming.[10] Although it has been stated that guanethidine in doses of 15 to 30 mg. per kilogram of body weight does not affect the blood pressure of normal dogs,[1] later reports indicated that with doses of 10 to 15 mg. per kilogram intravenously an immediate hypotensive phase was followed shortly by a rise in blood pressure which was maintained for several hours.[2,3] The latter reports[2,3] are confirmed in the present study. One example of the response to intravenous guanethidine is shown by Page and Dustan,[3] in which cardiac output increased from 2.5 to 4 liters per minute as measured by the electromagnetic flow meter. Similar

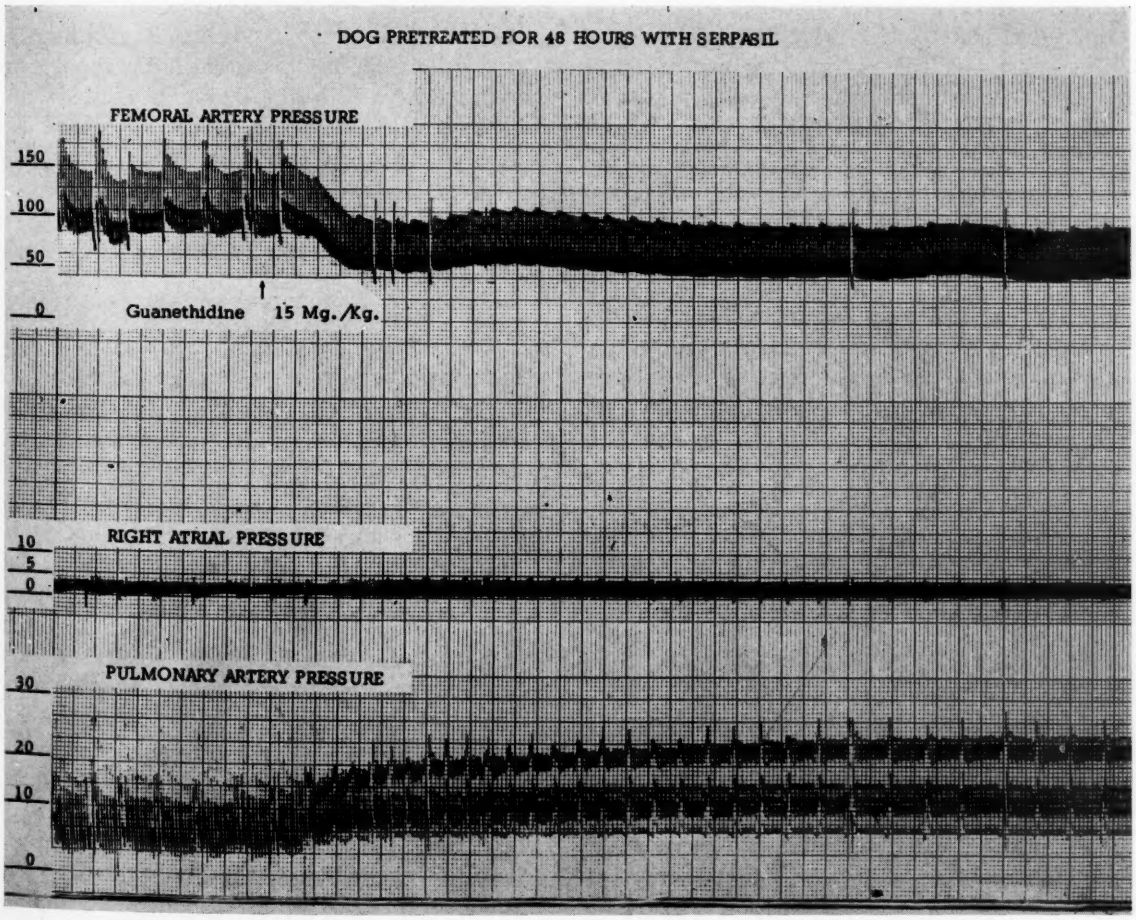

Fig. 2. A typical response of pressure is shown subsequent to the administration of guanethidine to a dog which had been pretreated for 48 hours with reserpine. This response may be contrasted with the response shown in Fig. 1.

examples of increased cardiac output are found in the present series, wherein the maximal increase was from 2.3 to 10.4 liters per minute. The response was, however, quite variable even though cardiac output increased in 11 of the 13 animals. The suggestion has been made that the administration of guanethidine is associated with a diminution in the available norepinephrine in the walls of the blood vessels[3] and in the heart.[11,12] Similarly, others have indicated[2] that the first several hours after administration of Ciba 5864-SU are characterized by very transient suppression of conduction from the preganglionic to postganglionic cervical sympathetic nerves, and a similar depression of vagal conduction, but of longer duration (4 hours +), followed during the first several hours after guanethidine by "strong sympathetic-like actions." These are predominantly the effects which have been measured in the present study. Maxwell and associates[2] concluded that "SU-5864 chronically interferes with the release and/or normal distribution subsequent to the release of the neurohumoral transmitter at the sympathetic neuromuscular junction." The presently reported fact that phentolamine may prevent or reverse the hypertensive response to guanethidine, as well as the fact that prior administration of reserpine will prevent the increase in cardiac output and the hypertensive response to acute administration of guanethidine, are both compatible with the suggestions that this phase of the action of guanethidine is due to the presence of catecholamines. Catecholamines are known to produce an increase in myocardial contractility,[6] arterial pressure, heart rate, hemoglobin concentration,[13] hematocrit, cardiac output, coronary blood flow, total body oxygen consumption, and myocardial oxygen consumption. Hence, these effects may well be attributed to the release of catecholamines from peripheral sites. Additional data have recently become available which indicate that subsequent to the administration of guanethidine the catecholamine content of the ventricular wall and aorta are reduced,[11,12] and that the effect of guanethidine is different when administered to a heart-lung preparation made from a dog which has been pretreated with reserpine or guanethidine.[14] These data reveal that the inotropic effect of guanethidine disappears in catecholamine-depleted specimens and are consistent with the presently reported rise in right atrial pressure after the administration of guanethidine in dogs pretreated with reserpine.

It is unfortunate that the stability of the animal preparation used in the present study is such that only the relatively short-term action of experimental agents may be studied. Consequently, hemodynamic information was not obtained during the prolonged depressor phase of guanethidine action. Such information is highly desirable in order to complete the hemodynamic picture of this agent, and the answer is strongly suggested by the data which indicate that heart-lung preparations from dogs pretreated with guanethidine respond to additional guanethidine in a manner very similar to that of the heart-lung preparations of dogs whose catecholamines have been depleted by chronic administration of reserpine.[14] Preliminary reports in man indicate that cardiac output is unchanged or increased[7] and somewhat reduced[15] during the hypotensive phase, and suggest that additional studies are needed. Renal blood flow is reported to be reduced in man subsequent to therapeutic doses of guanethidine.[15]

In the light of all information to date, a working hypothesis may be that on acute intravenous administration of guanethidine there is transient sympathetic and parasympathetic blockade, accompanied by transient hypotension and followed by more prolonged vagal blockade accompanied by sympathetic-like overactivity. This sympathetic-like overactivity is related to the release of catecholamines and is associated with hemodynamic effects typical of those of catecholamines. After a variable period of hours the sympathetic overactivity disappears, and effects of peripheral sympathetic blockade with depletion of catecholamines become apparent. This third, or prolonged hypotensive phase, may last from 48 to 96 hours after administration of the drug.[9] The response to the acute administration of guanethidine is different, therefore, in the catecholamine-depleted subject than in the normal subject.

Table I. *General effects of guanethidine*

	Before	*After*	*% Change*	*p Value <*
Cardiac rate	79	113	+43.0	0.001
Mean arterial blood pressure	119	137	+15.1	0.001
Mean pulmonary arterial blood pressure	14	20	+42.9	0.001
Mean right atrial pressure	3.2	3.9	+21.9	0.1
Minute volume of respiration	2.6	2.9	+11.5	0.1
Oxygen consumption	115	140	+21.7	0.001
CO_2 excretion	93	112	+20.4	0.001
Body respiratory quotient	0.81	0.80	− 1.2	0.5
Arterial hemoglobin	14.4	17.1	+18.8	0.001
Arterial hematocrit	44	54	+22.7	0.001
Arterial pH	7.25	7.19	—	0.001
Coronary sinus pH	7.21	7.17	—	0.01
Arterial O_2	17.6	19.7	+11.9	0.02
Δ A-V O_2	4.3	3.4	−20.9	0.05
Pulmonary arterial CO_2	52.5	48.8	− 7.0	0.001
Δ PA-A CO_2	3.1	2.2	−29.0	0.02
Coronary sinus O_2	5.1	5.6	+ 9.8	0.5
Δ A-CS O_2	12.3	13.9	+13.0	0.1
Coronary sinus CO_2	58.6	55.6	− 5.1	0.01

Table II. *Hemodynamic effects of guanethidine*

	Before	*After*	*% Change*	*p Value <*
Cardiac output (L./min.)	2.8	4.8	+ 71.4	0.02
Left ventricular work (Kg.M./min.)	4.4	9.1	+106.8	0.01
Right ventricular work (Kg.M./min.)	0.5	1.4	+161.5	0.01
Total peripheral resistance (c.g.s. units)	3,733	2,741	− 26.6	0.02
Total pulmonary resistance (c.g.s. units)	433	378	− 12.7	0.3
Coronary blood flow (m1./100 Gm./min.)	84	143	+ 70.2	0.01
Coronary vascular resistance (units)	1.5	1.1	− 26.7	0.01
Cardiac O_2 usage (m1./100 Gm./min.)	10.3	18.8	+ 82.5	0.001
Cardiac respiratory quotient	0.78	0.74	− 5.1	0.4
Index efficiency	0.44	0.49	+ 11.4	0.4

Table III. *Effects of guanethidine on 6 dogs pretreated with reserpine*

	Control	*Drug*	*S.E.M. Difference*	*p Value <*
Heart rate	74	122	8.727	0.01
Mean systemic arterial blood pressure (mm. Hg)	97	82	7.388	0.1
Mean pulmonary arterial blood pressure (mm. Hg)	17	22	2.122	0.1
Mean right atrial blood pressure (mm. Hg)	2.9	4.0	0.606	0.2
Oxygen consumption (ml./min.)	100	96	9.647	0.7
Arterial oxygen (ml./100 ml.)	16.4	17.6	0.471	0.02
Arteriovenous O_2 difference (ml./100 ml.)	4.7	4.0	0.457	0.2
Arterial hemoglobin	14.0	14.9	0.258	0.02
Arterial hematocrit	43	47	1.111	0.05
Cardiac output	2.2	2.7	0.592	0.4
Left ventricular work (Kg.M./min.)	2.8	3.1	0.632	0.6
Right ventricular work (Kg.M./min.)	0.5	0.9	0.342	0.3
Total peripheral resistance (c.g.s. units)	3,811	2,791	731.4	0.3
Total pulmonary resistance (c.g.s. units)	632	844	308.1	0.6

Summary

1. Guanethidine was administered intravenously in a dose of 15 mg. per kilogram of body weight to a series of dogs, and hemodynamic studies were performed before and an average of 22 minutes after its administration.

2. Subsequent to administration of guanethidine there was an increase in cardiac rate, hemoglobin, hematocrit, and mean arterial blood pressure in the systemic arteries, pulmonary artery, and right atrium, as well as an increase in cardiac output, coronary blood flow, and left ventricular oxygen consumption.

3. The increase in systemic arterial blood pressure subsequent to the administration of guanethidine was blocked by immediate prior administration of phentolamine, and the elevated pressure which resulted from guanethidine was reduced by the administration of phentolamine.

4. Pretreatment of the dog with reserpine prevented the hypertensive phase of guanethidine action, as well as the usual increase in cardiac output and body oxygen consumption.

5. These results are compatible with an increased sympathetic-like action during the intermediate phase of guanethidine action, and suggest that this phase could be due to the release of catecholamines.

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Case reports

Reticulum cell sarcoma of the heart simulating viral pericarditis

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Patients with malignant involvement of the heart may present with vague constitutional symptoms, intractable heart failure, disturbances of rhythm, coronary occlusion,[1] or pericardial effusion. A recent experience with a case mimicking benign viral pericarditis prompted this report.

Case report

A 79-year-old white woman developed pain in the left shoulder anteriorly and under the left breast, chiefly at night. The pain moved to the left shoulder posteriorly, and dry cough developed. Nocturnal rise in temperature to 100.5°F. was noted. When she was examined, tachycardia was found; an electrocardiogram showed only prolongation of the Q-T interval (QT_c 0.45 sec.). X-ray examination of the chest showed marked increase in the size of the heart shadow. She was referred to Beth Israel Hospital. There were no symptoms of congestive heart failure. Anorexia and loss of weight were denied. The patient had had no previous cardiopulmonary complaints and had enjoyed good health all her life except for painful osteoarthritis.

On admission to Beth Israel Hospital, temperature was 100.4°F., the pulse was 100 and regular, and the blood pressure was 120/80 mm. Hg. The patient was comfortable lying flat in bed, and she did not appear to be chronically ill. The neck veins were flat. Basal râles were present, which cleared when the patient coughed. The heart was slightly enlarged to percussion, and the sounds were distant. The second aortic sound was louder than the second pulmonic sound. A Grade 1 apical systolic murmur was heard. The liver and spleen were not palpable; there was no adenopathy and no peripheral edema.

Urinalysis was negative. Hemogram revealed: hemoglobin, 9.9 Gm.; erythrocytes, 2.67 million; leukocytes, 5,400, with 71 neutrophils, 24 lymphocytes, 2 eosinophils, and 3 monocytes. Erythrocyte sedimentation rate was 80 mm. in 1 hour (Westergren). An electrocardiogram showed a sinus arrhythmia, normal QRS voltage, but low T waves. No other abnormality was noted. A roentgenogram of the chest (Fig. 1) showed a left pleural density and marked cardiomegaly. The pulmonary vessels were not unusually prominent. Fluoroscopy confirmed the impression of pericardial effusion. Pulsations of the cardiac silhouette were minimal. The esophagus was displaced posteriorly by the heart. The patient was thought to have a pericardial effusion, due presumably to a viral pericarditis. She was treated with antibiotics and analgesics. For 2 days after her admission the temperature rose to 101°F. in the afternoon. Thereafter, the temperature was normal. The pain disappeared and a roentgenogram (Fig. 2) revealed disappearance of the pericardial effusion.

The patient went home feeling well and remained asymptomatic for 12 months. Then sternal discomfort, unrelated to effort or eating, appeared. Cough recurred. There was no dyspnea, but there was weakness and anorexia. After 2 months, dyspnea and pain in the right shoulder developed. A recurrent pericardial effusion plus a right pleural effusion were noted. The patient was given digitalis and mersalyl (which produced considerable diuresis), and she was readmitted to the hospital.

She appeared pale and in some respiratory distress. Blood pressure was 100/60 mm. Hg; pulse was 108 and regular. She was afebrile. There was no adenopathy. There were dilated veins over the upper anterior chest, which filled from below. Signs of right pleural effusion were noted. The heart was enlarged to just beyond the left mid-clavicular line. Auscultation indicated nothing remarkable. A firm, nontender liver was noted; the edge was felt 3 cm. below the costal margin. The spleen was not felt. There was mild pretibial edema. Urinalysis, hemogram, nonprotein nitrogen, blood sugar, and serum

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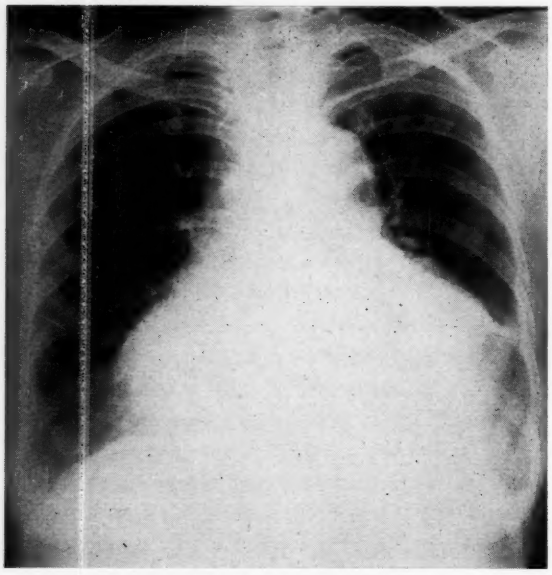

Fig. *1.* Original chest x-ray film showing large pericardial effusion.

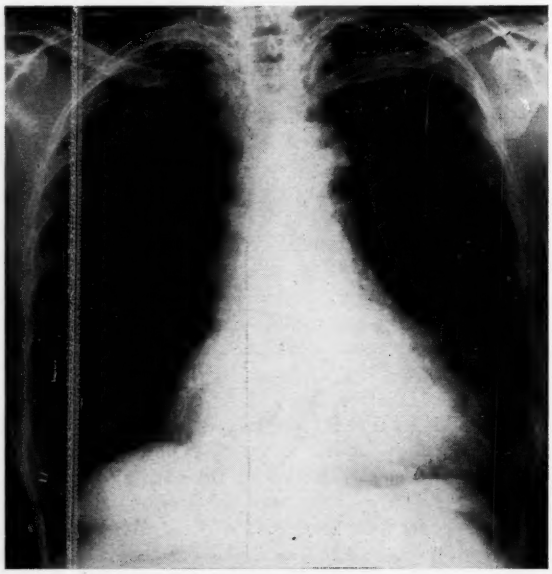

Fig. *2.* Chest x-ray film taken 1 month after Fig. 1. Pericardial effusion has been absorbed.

electrolytes were now within normal limits. The electrocardiogram showed an atrial tachycardia and digitalis effects. A chest film (Fig. 3) confirmed the impression of right pleural effusion and revealed an abnormality of the cardiac configuration. The venous pressure was 120 mm. of water, rising to 200 mm. on right upper abdominal pressure. Thoracentesis yielded 200 c.c. of straw-colored fluid, in which no malignant cells were found. Within a week the patient went into coma. She was treated with digitalis and mersalyl. She died on the fifteenth hospital day.

Postmortem examination, done by Dr. William Antopol, demonstrated reticulum cell sarcoma extensively involving the pericardium, both atria, and the left ventricle, with gross involvement also of the mediastinal, para-aortic, peripancreatic, and mesenteric lymph nodes. There was extension through the diaphragm and invasion of the left lobe of the liver. Five hundred cubic centimeters of clear amber fluid was found in each pleural space. The pericardial space, however, was obliterated by adherence of the epicardium to the involved pericardium, which measured up to 4 cm. in thickness (Fig. 4). The tumor filled and obstructed the coronary sinus, but the venae cavae were patent. There was extensive necrosis of tumor tissue in the heart and pericardium. Microscopic evidence of infiltration was noted in the gall bladder, Fallopian tubes, omentum, and serosa of the large bowel. The marrow and spleen did not contain tumor.

An old recanalized occlusion was found 2 cm. from the origin of the right coronary artery. An old calcified tuberculous complex was present in the right upper lobe.

Discussion

The tenth case of reticulum cell sarcoma of the heart was reported in 1957, by Kaufman and Cohen.[2] It seems unproductive to debate whether or not the heart was the primary site of tumor in the present case, especially since reticulum cell sarcoma may perhaps be of multicentric origin. The heart, however, was clearly the most extensively involved organ. Prichard,[3] in his review of 150 cases of cardiac neoplasms, states that "fibrinous pericarditis is often associated with tumor involvement of the epicardium." Other authors[4,5] (Grewin, Barnes) also refer to pericarditis

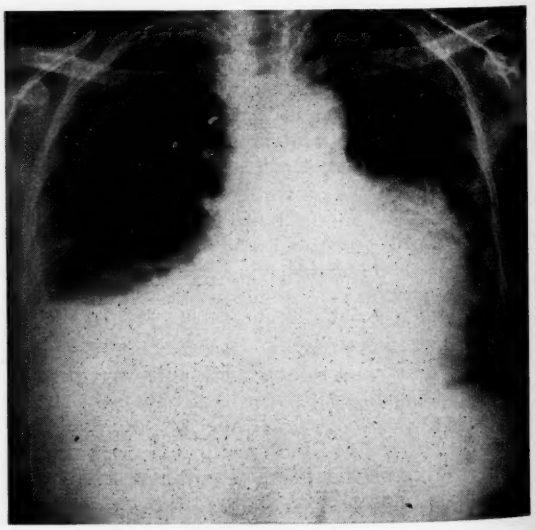

Fig. *3.* One year later. Recurrent pericardial effusion, right pleural effusion, and abnormal left cardiac contour.

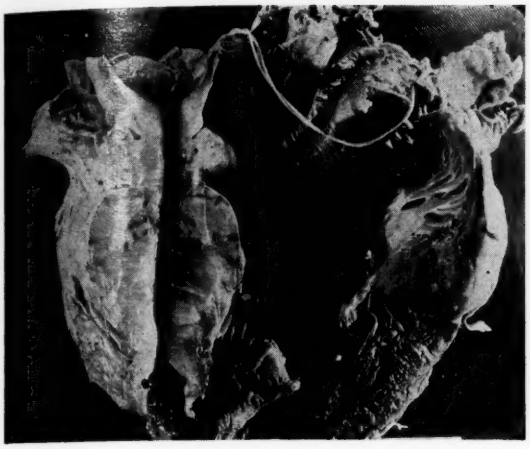

Fig. *4.* Uninvolved myocardium at lower right. Above it, sarcoma.

complicating cardiac malignancies. We have found only one previous case, however, in which pericardial fluid due to a sarcoma subsided spontaneously, only to recur later.[6]

There is also a report of a transient pericardial effusion from pericardial metastases from a squamous cell carcinoma of the trachea,[7] and another report of spontaneous decrease in a pericardial effusion due to pericardial mesothelioma.[8] Nabarro[9] reported transient pericarditis with effusion in a man who died of Hodgkin's disease that involved the heart.

It is conceivable that a coincidental viral pericarditis occurred a year prior to the patient's final illness, but the coincidence would surely be astounding. It is possible, too, that some latent virus was activated by the tumor present in the heart and pericardium, comparable to the appearance of herpes zoster virus in the distribution of a nerve when the nerve root is infiltrated with lymphoma, or similar to the appearance of herpes simplex virus in a previously sensitized area under a variety of stressful stimuli. There is no evidence to support this supposition, and it is unfortunate that no viral studies were performed.

No evidence of collagen disease or rheumatic fever was noted, either clinically or at autopsy. In 1956, Dressler[10] observed pericardial and pleural effusion in patients who had suffered myocardial infarction. He noted that a similar syndrome may occur in patients after commissurotomy, and believed that the condition represented "a particular reaction to necrosis of the myocardium." This belief is hypothetical; the cause is not known. The facts that tumor cells were not found in the pleural fluid of our patient, and that extensive necrosis was present in the tumor and in adjacent myocardium suggest that tumorous involvement of the heart may be another situation in which pericarditis and pleuritis result from cardiac damage. The old occlusion of the right coronary artery could hardly account for a postmyocardial infarction syndrome, since it was surely quite old, and the sarcoma was recent and aggressive.

A clinician observing a patient with an apparently benign viral pericarditis must consider the diagnosis of cardiac neoplasm —since surgical techniques may soon be available to deal more radically with malignant disease of the heart.

Summary

A case of reticulum cell sarcoma involving the heart is reported. The presenting picture originally was that of a pericarditis with effusion, and apparently a cure was effected after a few weeks. One year later the pericardial effusion returned, in association with substernal pain. Rapid death followed.

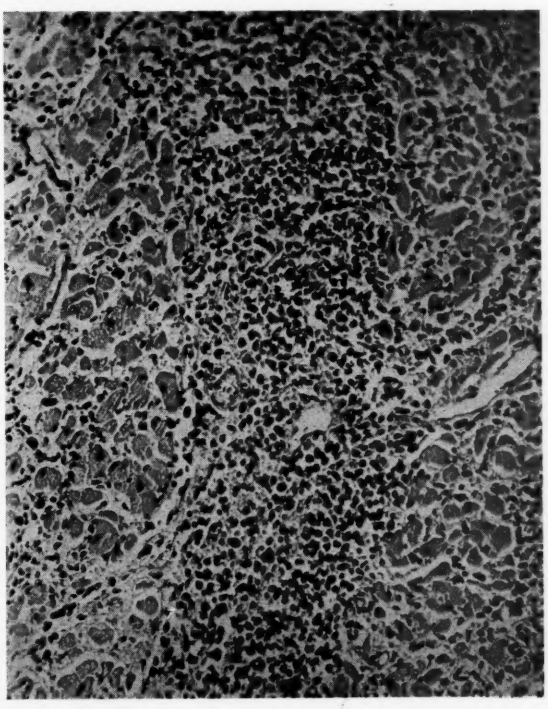

Fig. *5.* Microscopic appearance of tumor.

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Extracardiac influences on the electrocardiogram in organic heart disease
Observations on a patient with myocarditis

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A normal electrocardiogram by no means excludes heart disease, and abnormal tracings do not necessarily indicate an abnormal heart. Special caution is needed when interpreting departure from the assumed normal of the S-T segment and the T wave. Except for the known myocardial disease states which produce S-T and T abnormalities, it is essential to realize the wide range of normal variations and the abnormalities which may be induced by extracardiac influences.[1-3] These latter are: the position of the heart on the diaphragm (influenced by obesity, pregnancy, change in posture, and respiration), the effect of drugs, including nicotine, electrolyte imbalance, hyperventilation,[4] imbalance of the autonomic nervous system,[5] cold, fear, anxiety, fever, drinking of ice water, and meals.[6-10] The electrocardiographic changes induced by these factors revert to normal soon after the stimuli are removed, and they are often denoted as being functional in nature. The mechanism and significance of these changes are mainly obscure. It is widely assumed, however, that they are without clinical significance.

Relatively little interest has been focused on the influence of extracardiac factors on the electrocardiogram in established heart disease. The electrocardiographic changes induced in the patient reported here are similar to those characterized as functional. The evidences presented, however, are highly suggestive of organic heart disease, viz., myocarditis.

Case report

The patient was a 23-year-old military serviceman who had been previously in good health. He gave no history of rheumatic fever or dyspnea on exertion. On Oct. 11, 1959, he became acutely ill with chills, fever, and headache. During the subsequent days he developed a sore throat and general exanthema and became jaundiced. On admission on October 17, the examination revealed a well-developed man of athletic build. He was moderately jaundiced and there was a pink maculopapular exanthema localized mainly to the trunk. His chief complaints were headache, muscular stiffness, and a sore throat which rendered peroral supply extremely difficult. Clinical signs of dehydration were present, and his general condition was moderately deteriorated. The temperature was 38.2°C. The pulse was regular and 88 per minute. The blood pressure was 135/75 mm. Hg and remained in the same range during the illness. Clinical examination of the heart on admission gave normal findings. There was a marked bilateral, necrotic tonsillitis, with a thick, yellow exudate, and a bilateral enlargement of the cervical lymph nodes. The liver and the spleen were moderately enlarged. There was no clinical sign of involvement of the central nervous system.

Laboratory findings. The hemoglobin content was 13.4 Gm. per 100 ml. The red blood cell count was 4.1 million per cubic millimeter, and the white blood cell count was 13,100 per cubic millimeter. Differential blood count showed 60 to 70 per cent of the white cells to be atypical lymphocytes with a large, slightly bilobed nucleus. The sedimentation rate according to Westergren was 23 mm. per 1 hour.

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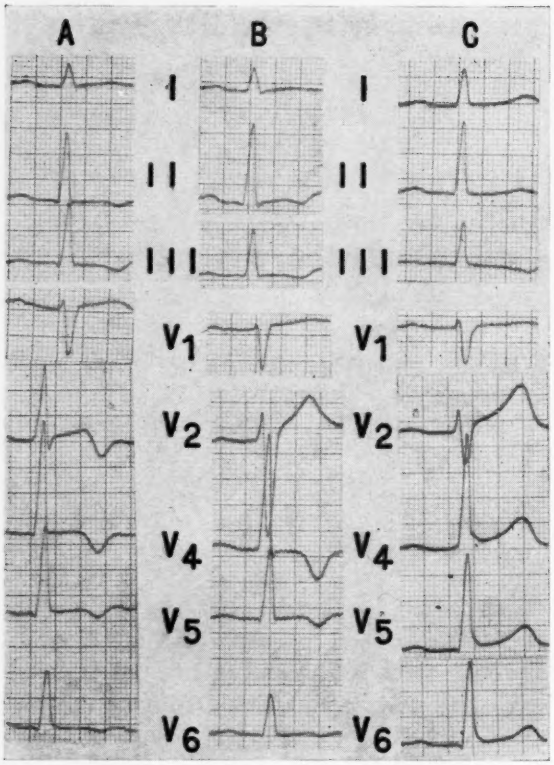

Fig. *1.* The electrocardiograms obtained in the fasting state on the first (*A*), the fourth (*B*), and the twelfth (*C*) days in the hospital.

The serum bilirubin concentration was 7.3 mg. per 100 ml. The thymol turbidity test was positive. The serum level of alkaline phosphatase was 14 Bodansky units. The plasma concentration of prothrombin and proconvertin according to Owren and Aas was 62 per cent of the normal. The serum glutamic oxalacetic transaminase (SGOT) level was 120 units. Paper electrophoresis of the serum proteins was normal. The plasma creatinine concentration was 1.0 mg. per 100 ml. Three blood cultures were negative. Two throat cultures were negative for streptococci but revealed staphylococci which were sensitive to penicillin. The serum antibody tests for Weil's and Bang's diseases were negative. The serum titers of antistreptolysins and cold agglutinins were in the normal range. There was a positive heterophil antibody agglutination (Paul-Bunnell test) which occurred in a dilution of 1 in 80. Urinalysis was negative except for a positive Harrison test. The spinal fluid was normal.

Diagnosis. The findings of fever, exudative tonsillitis, glandular enlargement, general exanthema, and clinical and biochemical signs of hepatic and splenic involvements were suggestive of infectious mononucleosis. The diagnosis was confirmed by the peripheral blood count and the positive Paul-Bunnell test.

Course. During the first hospital week the clinical condition remained unaltered. On the tenth day in hospital there was a sudden fall in the temperature. From then on he made a rapid and complete recovery. During the next week the sore throat cleared up and the exanthema and the icterus disappeared. Gradually, the glandular enlargement subsided and the liver and spleen could no longer be felt. Determination of SGOT was made daily. It was normal from the eleventh hospital day. The other biochemical signs of hepatic dysfunction were normalized during the following 2 weeks. The pathologic blood picture remained unaltered during his hospital stay. The patient was discharged in a good general condition 28 days after his admission. The peripheral blood smear examined 2 months later when the patient was on ambulatory control was perfectly normal.

Cardiovascular examination. On admission the pulse was regular. The blood pressure was normal by frequent measurements. No sign of congestive heart failure was present. The physical examination of the heart was normal.

Moderate clinical signs of cardiac involvement were present from the fourth to the twelfth day in hospital. Dull and remote heart sounds were observed during this period. At the apex there was a soft, systolic, Grade 2 murmur associated with a gallop rhythm. The second pulmonary sound at the base was exaggerated and reduplicated. No friction rub was observed. There was no clinical sign of pulmonary congestion. The abnormal findings by physical examination of the heart were normalized during the first few days after the temperature fell. During the acute stage, as well as during the convalescent stage, the roentgenologic examination of the heart was normal.

The patient has been followed regularly with clinical and electrocardiographic controls for 1½ years. There have been no symptoms or signs of heart disease.

Electrocardiographic studies. Fig. 1 shows the electrocardiograms taken with the patient in the fasting state on the first, fourth, and twelfth days after admission. In *A* and *B* of Fig. 1 there are negative T waves in the standard lead II and in the unipolar chest leads V_3–V_6. In *C* of Fig. 1 these are restored to normal. From the twelfth hospital day, i.e., 2 days after the fall in temperature, the electrocardiogram taken in the fasting state remained normal. However, for a transient period of 7 days, abnormal T waves in the unipolar chest leads were inducible by various measures. The evidences are given in Fig. 2. Only the unipolar chest leads V_3 to V_6 are reproduced. The changes in the standard leads and in the unipolar limb leads were insignificant.

Electrocardiographic changes induced by meals and by intravenous injection of glucose. Fig. 2,*A* shows the electrocardiogram obtained when the patient was in the fasting state. This remained normal during the days on which the following studies were performed. Fig. 2,*B* shows the electrocardiogram taken 20 minutes after the patient had eaten an ordinary breakfast. Distinct T-wave changes are present. Similar changes are induced by the patient ingesting 60 Gm. of glucose in 150 ml. of tap water (Fig. 2,*C*). In this case the changes appeared earlier. The electrocardiographic changes induced by meals persisted for a period of 60 to 120 minutes. Fig. 2,*D* shows the electrocardiogram 17 minutes after an intravenous injection of 40 ml. of 50 per cent glucose. The changes appeared in a few minutes after the injection and lasted for 35 minutes. The T-wave changes induced

by these measures were prevented when 4 Gm. of potassium chloride were ingested with a glass of water 30 minutes prior to the meal or the injection. It could also be demonstrated that the T-wave changes induced by a meal or an injection of glucose were abolished in 4 to 5 minutes after an intravenous injection of 0.5 mg. of dihydroergotamine.

Electrocardiographic changes induced by drugs and nicotine. Fig. 2,*E* shows the electrocardiogram which was recorded 8 minutes after the patient had received a subcutaneous injection of 0.5 mg. of Adrenalin in the fasting state. The T-wave changes were at this time maximal. They lasted for 30 minutes. The changes were not preventable by peroral potassium. Fig. 2,*F* shows the electrocardiogram 7 minutes after the patient was given an intravenous injection of 1 mg. of atropine in the fasting state. Potassium did not prevent the changes from occurring. Fig. 2,*G* shows the electrocardiogram recorded when the patient was smoking a cigarette in the fasting state. The patient was a habitual smoker. The T-wave changes appeared in a couple of minutes and lasted for 5 to 10 minutes after he stopped smoking. The changes induced by nicotine were readily abolished by an intravenous injection of 0.5 mg. of dihydroergotamine. They were not prevented by potassium given by mouth.

The electrocardiogram remained uninfluenced by the following: drinking of ice water, distending the stomach with effervescent powder given by mouth, the respiration phase, the posture of the body, and heavy muscular work.

These electrocardiographic changes were only inducible during the first week after the fall in temperature. Later on, the normal electrocardiogram in the fasting state remained completely uninfluenced by the above-mentioned states. For the subsequent 1½ years, regularly obtained electrocardiograms re-

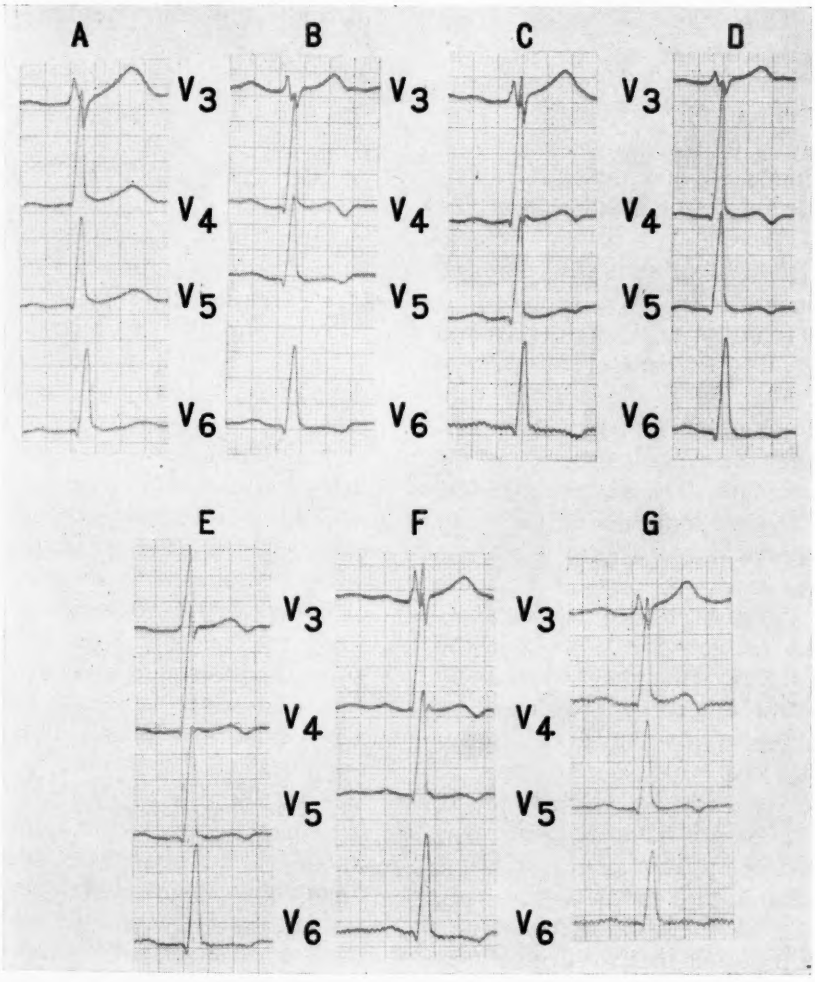

Fig. 2. The electrocardiographic changes in the period from the twelfth to the eighteenth days in hospital induced by various measures. *A:* Fasting state. *B:* 20 minutes after breakfast. *C:* 15 minutes after 60 Gm. of glucose ingested in a glass of water. *D:* 17 minutes after an intravenous injection of 40 ml. of 50 per cent glucose. *E:* 8 minutes after a subcutaneous injection of 0.5 mg. of Adrenalin. *F:* 7 minutes after an intravenous injection of 1 mg. of atropine. *G:* 5 minutes after the start of smoking a cigarette.

corded under various experimental conditions, including fever induced by typhoid vaccine, have remained normal.

Discussion

The occurrence of cardiac involvement in infectious mononucleosis is well documented.[11-15] This rarely will be severe enough to cause more than transient electrocardiographic abnormalities. At autopsy, perivascular lymphocyte infiltration, focal interstitial collections of mononuclear cells, as well as muscular necrosis have been reported.[16-18]

In the case reported upon here there were reasonable clinical, laboratory, and electrocardiographic evidences to suggest infectious mononucleosis with myocardial involvement. The nature of this process remains open for discussion. The electrocardiographic pattern during the acute phase of the illness might suggest a profound myocardial damage. Because of the associated hepatic involvement, it is impossible to reach any conclusions from the elevated SGOT level.

Transitory electrocardiographic changes induced by meals have been reported in normal individuals as well as in patients with coronary heart disease.[6-10,19] These usually consist of S-T depressions and flattening or inversion of the T waves. Rarely are they so distinctly present as in the reported case. The nature of these changes and the explanation of their occurrence in particular subjects only are not clear. It is widely assumed that these changes are without clinical significance. It has been stated previously[9,10] that the electrocardiographic changes induced by meals or glucose might be prevented by peroral potassium salts. It has been demonstrated here that this also might apply to the changes induced by intravenously administered glucose. This suggest that the electrocardiographic changes in some way are related to the potassium metabolism, probably to the shift of potassium from the extracellular to the intracellular myocardial space, a process which is influenced by a raised level of glucose in the blood and an increased activity of insulin. The electrocardiographic changes induced by meals and by glucose injected intravenously were readily abolished by dihydroergotamine. These findings might be explained in two ways. The effect on the electrocardiogram of meals and glucose might be related to an increased sympathetic tone which sensitizes the myocardium to the shift in potassium. Another possibility is that the shift of potassium ions is the primary mechanism which renders the myocardium especially sensitive to sympathetic influences.

It has previously been suggested that the electrocardiographic changes induced by nicotine might be related to an increased sympathetic tone.[20] The effect of dihydroergotamine during smoking which was observed in this case supports this view. Neither the electrocardiographic changes induced by nicotine nor those elicited by atropine and Adrenalin were preventable by peroral potassium salts. Thus, there were evidences to suggest that the electrocardiographic changes induced in this case were mainly dependent on an increased sensitivity to adrenergic impulses or transmitters.

The reported electrocardiographic features are in accordance with those characterized as being functional in nature, i.e., without organic correlates and therefore without clinical significance. Electrocardiographic patterns of this kind have been ascribed to an increased sympathetic tone,[5] and individuals in whom such changes are demonstrated often present additional clinical signs of vegetative dysfunction. However, in the case presented, there were clinical and electrocardiographic evidences of myocardial involvement. This is emphasized by the fact that the electrocardiographic abnormalities were inducible only during a short transient period after the acute infectious phase. Therefore, whereas the electrocardiographic patterns denoted as functional probably are related to an increased sympathetic tone, the electrocardiographic changes in the case reported upon were presumably dependent on structural damage which increased the myocardial sensitivity to adrenergic impulses or transmitters, or produced a shift of the vegetative tone of the heart in a sympatheticotonic direction.

Summary

A report is made on a 23-year-old man with infectious mononucleosis in whom

there were clinical and electrocardiographic evidences of myocardial damage during the acute phase of the illness. He made a rapid and complete recovery. During the early postinfectious phase, transient electrocardiographic changes could be elicited. These consisted of inversions of the T waves in the unipolar chest leads which were inducible by various measures: an ordinary breakfast, 60 Gm. of glucose in a glass of water, hypertonic glucose given intravenously, smoking a cigarette, atropine given intravenously, and Adrenalin given subcutaneously. The changes induced by meals and glucose were preventable by potassium chloride given by mouth, whereas potassium was without effect on the changes induced by other means. The electrocardiographic changes induced by meals, glucose given intravenously, and nicotine were readily abolished by an intravenous injection of dihydroergotamine. It is suggested that the transient electrocardiographic changes induced in this patient were related to structural damage, probably myocarditis, which increased the muscular sensitivity to adrenergic impulses or transmitters. It is emphasized that transient electrocardiographic changes induced by extracardiac influences, which one might characterize as being functional in nature, may be a sign of organic heart disease.

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Review

The renin-angiotensin* system in hypertension

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The possibility that human hypertension could be explained on a renal basis was generally accepted after Goldblatt and associates[1] were able to produce in the dog by partial occlusion of the renal arteries a type of hypertension, the hemodynamic aspects of which are very similar to those of human hypertension.

Subsequent experiments showed that this hypertension could not be prevented by renal denervation[2]; that grafting the ischemic kidney from a renal hypertensive dog into the neck of a normal dog produces a rise in blood pressure in the recipient[3]; that blood taken from the vein of the ischemic kidney of a hypertensive dog has higher vasoconstrictor activity than does that taken from the renal vein of a normal dog[4]; and that a renal enzyme, renin,[5] acting on a plasma globulin produces a pressor polypeptide which has been named *hypertensin*,[6] *angiotonin*,[7] or *angiotensin*.[8]

From these experiments it became apparent that this type of hypertension was humoral and probably mediated by an increase in the renin-angiotensin system.

More than twenty years have passed and we are still wondering what the role of the renin-angiotensin system is, and what are the possibilities of this being the mechanism responsible for hypertension.

Several reviews have been written on this theme, most of which seem to indicate that this humoral mechanism is responsible for, at least, experimental hypertension.[9-11] There are other papers, however, that throw doubt on this interpretation.[12-15]

It is our purpose to evaluate some of the latest evidence for and against the renin-angiotensin hypothesis.

Hypertension may be explained by the renin theory if an increase in renin or angiotensin is found in the hypertensive animal or man, due either to an increased production or a diminished destruction. These possibilities will be discussed in relation to: (a) renin and (b) angiotensin.

Renin

I. Direct evidence.

A. CONTENT. The amount of renin in the kidney and in the blood has been measured in dogs before and at different intervals after partial occlusion of the renal artery.[12] The renin content of both the blood and the kidney has been found to be increased during the first 10 days after the application of the clamp. This increase was more marked in the first week than in the second. After this period the renin content returned to normal levels. Similar results were obtained in the rabbit.[16]

In rats which developed hypertension after unilateral clipping, with untouched contralateral kidney, it was found that the

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*In this article, hypertensin [6] or angiotonin [7] will be called *angiotensin*, as suggested by Braun Menendez and Page,[8] with the hope that this will be the standard uniform nomenclature used in the future.

renin content of the clipped kidney was either slightly lower[17] or slightly higher[19] than that of normal controls, or was normal,[18] whereas the renin content of the contralateral kidney was uniformly found to be diminished.

These experiments[17-19] suggest that the *total renin content*, if it is possible to use this term for the sum content of both kidneys, is normal or below normal. If the plasma level of renin is a representation of the level of renin in the kidney, these experiments would also be in agreement with previous findings of a decreased renin content of the plasma in hypertensive rats.[20]

Several attempts have been made in man to demonstrate an increase in the renin content in patients with essential or malignant hypertension. Initial investigations showed that the renin content of blood coming from the renal vein was not significantly different in hypertensive subjects from that in normal subjects.[21] Nor was there any difference in the renin content of the systemic blood in either group,[13] or in biopsies taken from kidneys in normal and hypertensive subjects.[14] More recently, Peart[15] was unable to detect any traces of renin coming from the renal vein of hypertensive subjects, although his method is known to be capable of detecting this substance when the blood pressure is elevated by an infusion of renin.

Contrary to this, Haas and Goldblatt[22] claim that renin content is increased in all periods of hypertension. They found an increase in the "total renin content" in dogs which developed hypertension when one renal artery was clamped and the contralateral one was left untouched. They also found that the renin content of the kidney of hypertensive subjects was four times greater than that of normal subjects. The method used by them is not significantly different from that employed by others, so that there appears to be no satisfactory explanation for the discrepancy in the findings.

There is much evidence, both in animals and in man, that seems to indicate that the renin content of the kidney increases whenever there is an interference with the blood flow in the kidney and/or with the perfusion pressure of the kidney. Experiments which show that the renin content of the ischemic kidney of a hypertensive dog rapidly increases when it is perfused at a normal pressure[12] are in favor of this point of view. The renin content apparently decreases again to normal levels shortly after the blood flow in the kidney or the perfusion pressure of the kidney is restored. Moreover, elevation of the perfusion pressure of an isolated kidney for 1½ to 2½ hours produced a decrease of about 43 per cent in the juxtaglomerular index,[23] which has a good correlation with renin content.[24]

Evidence seems to indicate that the renin content or the liberation of renin is increased in the acute phase of renal hypertension, but in the chronic phase, as in essential hypertension, both content and liberation appear to be normal. Therefore, we must conclude that the experiments directed toward the investigation of renin content up to now give no support to the renin-angiotensin theory.

II. Indirect evidence.

A. EFFECT OF REMOVAL OF ISCHEMIC KIDNEY. It has been well established that in dogs,[25,26] rabbits, [27,28] and rats[29] with sustained experimental renal hypertension the blood pressure remains elevated after total nephrectomy until the animals die. On the contrary, in the early phase of experimental hypertension, removal of the ischemic kidney results in the normalization of the blood pressure.[27,28]

This evidence seems to indicate that in the early period of hypertension the ischemic kidney may be releasing a pressor substance, but is against this possibility in the late phase of hypertension. This conclusion is in accordance with the results obtained by direct measurements of renin.

B. EFFECT OF ADDING A NORMAL KIDNEY. Grafting a normal kidney into a hypertensive dog,[30] rat,[31] or man[32] results in a fall in the blood pressure. It was shown that this was not due to hemodynamic artifact, since grafting a leg or creating an arteriovenous fistula does not change the blood pressure. On the contrary, the grafting of a normal kidney does not lower the blood pressure of an animal in which the pressure is elevated by an infusion of renin or angiotensin.[31] This different behavior between chronic hypertension and that produced by

infusion of renin or angiotensin argues against the theory that hypertension is due solely to an increase in renin or angiotensin.

C. RENIN TACHYPHYLAXIS. Repeated injections of renin bring about progressively diminishing response.[5] This property, which is called *renin tachyphylaxis*, has been explained in various ways. The investigations seem to indicate that renin tachyphylaxis appears preferentially when the renin used is not highly purified, and if the blood pressure of the animal is not allowed to return to the starting level between injections.[33] Hemodynamic studies have shown that the blood pressure drops without any change in the cardiac output.[34] This indicates that during renin tachyphylaxis there is a lack of response of the arteriolar smooth muscles.

It has been shown that by continuous injection of renin it is possible to maintain a permanent elevation of the blood pressure.[35] Superimposed injection of renin in animals in which the blood pressure has been elevated by infusion of renin produces a drop in the blood pressure to normal levels, due to the appearance of tachyphylaxis.[36] On the contrary, in animals with ischemic renal hypertension, after repeated injections of renin the blood pressure remains at the hypertensive levels.[37] This difference is another argument against the possibility that experimental hypertension could be due only to a larger production of renin. Nevertheless, it has to be considered that the hemodynamic conditions in hypertension produced by continuous infusion of renin and those in hypertension due to renal ischemia are not absolutely comparable. In fact, the rise obtained by infusion is smaller than that seen in renal hypertension. Moreover, in the infused animal the response to superimposed injections of renin or angiotensin is lower.[35,37,38] In renal hypertensive animals it appears to be normal or increased.[39]

D. ANTIRENIN. The studies of Wakerling and his group,[40] which have been confirmed by others,[41,42] have shown that repeated injections of renin in dogs with acute or chronic experimental renal hypertension are followed by a drop in the blood pressure. This has been attributed to specific immunologic reactions. The possibility that this reaction could be due to a toxic nonspecific effect of the impure renin used has been suggested. Nevertheless, Wakerling was able to show that extracts of other tissues had no antihypertensive effect, and that the fall in the blood pressure appeared only when antirenin titers developed.

This work in antirenin constitutes the most important argument in favor of the renin theory. However, it should be emphasized that since the renin used in these experiments was not a pure protein, it still has to be proved that similar results could be obtained with purified renin.

E. CROSS-CIRCULATION EXPERIMENTS. Isovolemic cross circulation between chronically hypertensive and normal rats[43] did not produce any change in the blood pressure of the normal rat. Such a result would not be expected if the hypertension was produced by circulating renin, since cross circulation between a rat whose blood pressure was elevated by infusion of renin and a normal rat is followed by an increase in the blood pressure of the latter. Moreover, the method was also capable of detecting renin when the cross circulation was done between a normal rat and one in which the renal blood flow was restored after a period of 4 hours of complete bilateral ischemia. Under these circumstances it has been shown that the renin content is markedly increased.

Angiotensin

I. Direct evidence.

A. CONTENT. Even admitting a normal renin content, the possibility exists that angiotensin may be increased. The techniques for the measurement of angiotensin are more complicated than those used for the assay of renin, and this is probably one of the reasons why not many attempts have been made in this direction. The work of Skeggs and his group[44,45] has presented the main evidence in favor of an increase in angiotensin in experimental hypertension, both in the acute and chronic phases. They also support the theory that angiotensin could be the mediator of human hypertension. In fact, Skeggs' data in malignant hypertension show an increase in angiotensin content. However, his results for essential hypertension show a great overlap with findings in a normal control group.

The method used by Skeggs and associates requires a very large volume of blood. This represents a disadvantage since bleeding per se can produce an increase in the liberation of renin. With a new method developed recently by Scornik and Paladini,[46] which permits the detection of angiotensin in a small amount of blood, comparative studies of the angiotensin content of blood taken from normal and hypertensive animals have shown that there was no relationship between the amounts of angiotensin and the elevation of the blood pressure in dogs with experimental hypertension.

A critical analysis of the results does not allow one, at the moment, to accept an increase in the angiotensin in the blood either in the animals with experimental renal hypertension or in patients with essential hypertension. Nevertheless, the difficulties in the methods must again be emphasized. Therefore, additional studies are necessary before we can definitively accept or deny the existence of an increase in this pressor substance in the blood of hypertensive subjects.

II. Indirect evidence. Since the moment angiotensin was synthesized, attempts have been made to compare the dynamic behavior of chronically hypertensive animals with that of animals in which the pressure was elevated by means of an infusion of angiotensin. It has to be pointed out that these conditions are not truly comparable since the situation in established hypertension must be different from that of a temporary elevation. In fact, in chronic hypertension, some compensatory mechanisms appear, such as left ventricular hypertrophy[47,48] or changes in the regulation of the blood pressure, as for example, a resetting of the carotid sinus mechanism.[49,50]

A. CROSS CIRCULATION. As previously mentioned, cross circulation between a normal rat and a chronically hypertensive one does not produce changes in the blood pressure of the normal one. On the contrary,[42] if cross circulation is done between a rat in which the blood pressure has been elevated by infusion of angiotensin and a normal rat, an increase in the blood pressure of the latter is rapidly seen. As in the case of renin, this experiment is an argument against the possibility of the existence of a significant increase in the angiotensin content of the blood of the chronically hypertensive animals.

B. PITHING. Destruction of the central nervous system produces a drop in the blood pressure. By means of this procedure in a group of normal and hypertensive rats, it was found that the blood pressure fell in both to the same level after pithing.[51] On the other hand,[51] in animals in which the blood pressure was raised by infusion of angiotensin, after pithing the pressure also fell, but it remained at a higher level. Interruption of the infusion produced an additional drop in the blood pressure, which then reached the same level as that found in the other two groups. These experiments could also imply that angiotensin alone cannot be the cause of hypertension.

C. HEMODYNAMICS OF THE PULMONARY CIRCULATION. Early investigations[52] have shown that infusion of angiotensin elevates pulmonary arterial pressure. These have been used as an argument against the angiotensin hypothesis, since the pulmonary arterial pressure is normal in hypertensive men and animals.[53] More recently, it has been shown that synthetic angiotensin in doses of 2.5 to 15 gammas produces a rise in systemic and pulmonary pressure, with no change in cardiac output, and with a decrease in heart rate.[54] The percentage rise in the blood pressure with this dose was equal in both circulations.

Infusion of angiotensin in normotensive men[55] produced an increase in systemic, pulmonary, and wedge pressures, with no change in cardiac output. Calculation of the vascular resistance shows an elevation of the total pulmonary resistance, with normal pulmonary arteriolar resistance. This suggests that the action of angiotensin takes place distal to the pulmonary arterioles, either in the pulmonary veins, because of venous constriction, or in the left side of the heart, because of acute left ventricular failure. Recent experiments give additional support to this view. In fact, in dogs after single injections of 2 gammas per kilogram an increase in pulmonary and systemic blood pressure was found. Larger doses produced, at first, an increase in systemic blood pressure, and, subsequently, an increase in left

ventricular end-diastolic, wedge, and pulmonary pressures. As soon as the systemic blood pressure dropped, the left ventricular end-diastolic and wedge pressures returned to normal; the pulmonary arterial pressure remained 1 or 2 mm. Hg higher until the effect of angiotensin completely disappeared. The same patterns were seen during infusion of 4 and 1 gammas per kilogram per minute of angiotensin.[56]

In the face of these results, the elevation of the pulmonary pressure produced by infusions of angiotensin appears today to be a poor argument against the angiotensin hypothesis, since, if there is no change in the left ventricular end-diastolic pressure, the blood pressure rises only a few millimeters of mercury, remaining within the normal range.

D. ANGIOTENSINASE. Several attempts have been made to see whether a difference between levels of angiotensinase (the enzyme that destroys angiotensin) in normal and hypertensive animals could explain hypertension. Recent investigations[17] showed identical results in normal and renal hypertensive rats. This confirms previous experiments in dogs.[57] It seems unlikely, therefore, that lower destruction of angiotensin due to changes in the angiotensinase content could be the cause of hypertension.

Further comments

From the evidence previously presented, it can be concluded that the tempting hypothesis that hypertension is due to an increase in the renin or angiotensin content is still far from being proved.

Many contributions made during the last few years oppose this hypothesis. Nevertheless, there has to be acceptance of the fact that the methods used to measure renin and angiotensin are still unreliable, and, therefore, the evidence in favor of or against the existence of changes in the production, liberation, and destruction of the substances is not conclusive.

Recent studies have located the site of formation of renin in the vicinity of the glomeruli and the distal "tubuli contorti" in the region in which the juxtaglomerular cells are found.[24] Some investigations show that the changes in renin content of the kidney under different conditions may parallel the changes observed in the juxtaglomerular cells. These facts have given rise to the hypothesis that renin might be produced by these cells. There is also some evidence which suggests that renin may be important in the excretion of water and electrolytes,[58-60] more so than in the maintenance of the blood pressure during the chronic stage of hypertension. What is the exact role of the juxtaglomerular cells? What is the relationship between these cells and renin? What are the influences of osmotic and/or pressor variations on them? What is the exact role of renin in kidney function? All of these questions require additional research.

It seems that renin may play a role in the acute interference with blood flow and perfusion pressure in the kidney. Under these circumstances, renin content will increase, and probably through this mechanism the pressure will be elevated. But apparently other mechanisms, such as changes in vascular reactivity, changes in vascular structure, increase in neurogenic tone, etc., may be responsible for the maintenance of chronic hypertension.

Even if the importance of the renin-angiotensin system as mediator of hypertension appears to be disputable, the kidney still seems to be the place on which to focus attention in relation to chronic essential hypertension. In fact, ischemia of the kidney, in experimental animals as well as in man, is capable of producing a hypertension that is difficult to differentiate from human essential hypertension. This being so, it is hard to deny that angiotensin, the most active pressor polypeptide known, could be related to the maintenance of chronic hypertension.

The final answer to what role the renin-angiotensin system plays will require more investigation based on improved methods, and also on a better understanding of the normal and pathologic regulation of the blood pressure.

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Annotations

Isometric contraction and myocardial power

The concepts "effort" and "work" are easily confused. A man who keeps a heavy weight up may exert himself but he delivers no work in the physical sense *to the weight* (energy received equals force times path). Yet in the physical sense also much energy is being produced by the man. Compared with the resting condition, his metabolism is increased and the energy present in chemical compounds is converted into heat. This energy is given off to the surroundings; the larger the effort, the greater the amount of this dissipated energy will be.

When the man actually lifts the weight over a certain height, energy is delivered in both ways. It is delivered to the weight and in the form of heat to the surroundings. The effort will depend upon both amounts of expended energy.

When the left ventricle in a certain time ejects a volume V of blood against an average pressure p, the total amount of energy delivered by the heart muscle will likewise be = pV (work) + dissipated energy.

During isometric contraction no blood is ejected, V = 0, and the first term disappears. The energy needed to bring the pressure up to the value which can open the aortic valves is present in the second term, it is *not* as is sometimes said equal to the product of the diastolic pressure in the aorta and the volume of blood in the left ventricle. As a consequence, it is not physically justified to define myocardial power as the quotient of this product and the time duration of isometric contraction.

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Autoregulation of blood flow

The rate of blood flow through vascular beds tends to remain constant despite fluctuation of arterial pressure over the approximate range of 70 to 200 mm. Hg.[1-4] The regulation is highly efficient in the kidney,[5] slightly less efficient in the intestine,[6,7] moderately efficient in the heart,[8] and relatively inefficient in the limb.[9] The precise mechanism of the regulation has been the subject of many studies and debates.

It is clear that the mechanism resides within the bed because regulation is observed in the completely isolated organ.[10-12] Regulation is not an artifact of the methods,[13] because the kidney regulates even when untouched.[14] It is also clear that the regulation results from change in the caliber of the vessels rather than from change in the viscosity of the blood,[15] because regulation occurs during perfusion with artificial noncellular fluids.[12] However, a subject of much debate has been whether the change in caliber is passive, due to change in transmural pressure (rise or fall in tissue pressure due to capillary filtration or absorption subsequent to rise or fall in arterial pressure), or active, due to change in the contractile state of vascular smooth muscle within the wall of the vessel. Those who support the passive mechanism[11,16,17] observe, in association with renal regulation, a large change in tissue pressure, as measured through a large-bore needle plunged into the parenchyma,[11,16] and a large change in small venous pressure, obtained by retrograde venous catheterization.[16] These techniques accurately reflect tissue pressure and true lateral small venous pressure in the dog forelimb, but what they reflect in the kidney will remain unknown until the bleeding caused by the tissue needle[1] and the degree of vein-to-vein anastomosis distal to the wedge site of the venous catheter are thoroughly investigated. Those who support the active mechanism find that regulation is not associated with much change in the rate of flow of lymph from the kidney,[5] and that regulation disappears after inactivation of vascular smooth muscle (anoxic death, cyanides, etc.).[5,10,18]

There has been an intense search for the stimulus of an active response. The stimulus is not related to the nerve supply because regulation continues after section of extrinsic nerves,[5,10-12] blockade of circulating catecholamines and local sympathetic nerves,[5] or potentiation of local parasympathetic

nerves.[5] Neither does it seem to be related to carbon dioxide because the kidney continues to regulate after great elevation of carbon-dioxide tension.[5] Furthermore, carbon dioxide per se seems to have little local vasoactivity. There is some evidence which indicates that the response might be related to oxygen because this agent appears to have some local vasoactivity (constricting when tension is high and dilating when tension is low), and tissue oxygen tension might be expected to rise with an increase in the rate of flow and to fall with a decrease in the rate of flow. However, elevation of intraluminal pressure by partial venous obstruction with the rate of flow held constant produces evidence of an active response,[9] and, in this circumstance, oxygen tension does not change. Furthermore, isolated small arteries and strips of small arteries actively resist distention and extension, respectively.[19,20] Hence, it appears that autoregulation of blood flow results, at least in part, from active change in arteriolar caliber subsequent to some direct effect of change in transmural pressure upon the smooth muscle cell (myogenic response). This response, however, might be potentiated by changes in the concentrations of vasoactive metabolites.

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Errors encountered in records of the postexercise electrocardiogram

In 1932, Wood and Wolferth[1] first described changes in the postexercise electrocardiogram in patients with angina. Since then the use of the electrocardiogram after exercise to determine whether atypical chest pain is due to coronary disease, and even for the early diagnosis of preclinical coronary disease, has become increasingly popular, especially in recent years. For a time, it was of interest chiefly to life insurance companies and for the evaluation of cardiac integrity in industrial medicine when the

patient might fail to reveal symptoms. However, as a result of a statistical study by Robb, Mattingly and Marks,[2] there is evidence that the test has a prognostic value even with borderline or slightly positive results. This fact, coupled with growing knowledge regarding the possibilities of minimizing the progress of atherosclerotic heart disease, is leading to the more frequent use of the postexercise electrocardiogram in routine health examinations.

Approximately one third of the many postexercise electrocardiograms sent to our Medical Department are either useless or of limited value. This is due to the errors or inadequacies in the performance of the test. Here are the most common errors of procedure that we have encountered in reading records of the electrocardiogram taken after exercise:

1. Taking just one series of leads immediately after exercise. This is inadequate because the diagnostic changes occur frequently at periods of 2 to 3 minutes or more after exercise.

2. Using a single test,[3] that is, only 18 to 20 trips over the steps. This is frequently not enough unless the subject has a substantial amount of coronary insufficiency. Sometimes it is wise to do a single test as a precaution, but if this is negative, a double test must be done later.

3. A wandering base line due to a loose electrode or respiratory excursions, or both. This makes it impossible to measure S-T-segment depression.

4. Starting the recording too late after exercise. The patient must be placed on the bed at once after exercise, the cable plugged into the machine instantly, and the test started. Fumbling around for a minute or two after exercise can result in the loss of a positive response.

5. Recording too many leads after exercise on a one-channel machine. A rate of 100 or more in Lead I immediately after exercise may be seen to drop to 80 by the time Lead V_5 is taken because a full twelve-lead electrocardiogram was leisurely taken after exercise. This may result in a time lapse of 3 to 5 minutes. Here again this may result in the loss of a positive response. It is desirable to take Leads I, II, and possibly III very quickly within about 20 seconds, then Leads V_5, V_4, and V_2, in that order, in the next 30 seconds. This requires practice and team work involving two people, one operating the machine and one holding the electrodes. Of course, if a four-channel direct writer is available, it is possible, with proper practice and planning, to take the full twelve leads after exercise, but two people are still necessary to perform the test adequately.

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The cost of medical care

The cost of medical care and hospitalization combined with the "wonder" drugs is so expensive that we are constantly confronted with the problem of how to finance an operation, especially an open-heart operation, or a long chronic illness, such as subacute bacterial endocarditis or a staphylococcal infection.

Blue Cross and Blue Shield pay for hospital care for a limited period of time but, of course, do nothing to pay for outpatient or home visits. The State and Regional Health Programs sponsored by the Children's Bureau and by the Department of Health pay for the major part of the cost for a large number of children who are under 21 years of age. A number of labor organizations pay for the children of the worker. Nevertheless, there are many other patients for whom no help is available.

When one talks with men who have been in private practice and with the Armed Forces, one frequently hears that what is best about Army medicine is that the doctor is able to give the patient the care he needs. This is a real challenge to the medical profession.

Therefore, when in England last fall, I asked for the opportunity to discuss the British Health Service with some of the general practitioners. The evening opened with the comment that they did not think that the Health Service was fair to the wealthy because they both paid their share of the cost of medical care and, in addition, had to pay the private fees and the cost of illness. This, of course, is true of our educational system throughout this country.

The next point that the doctors brought up very emphatically was that the present English system did not allow them sufficient time to attend medical meetings or take refresher courses, or even give them the opportunity for vacation. The doctor's panels were too large to be turned over to another

physician. This, in their minds, was a real problem which needs to be solved.

The third point was that a poor doctor could make as much money as a good doctor. This is also possible under our system. It is not necessarily the best who earn the most. The fourth point to be brought out was that the doctors in England could not sell their practice as had previously been the custom—a custom which the English believed was a stimulus to building a good practice into an investment. This, however, does not concern us.

All of them *agreed* that (1) there was no government interference with their practice; (2) the paper work was not excessive; (3) they could give better care to their patients (all emphasized this); and (4) the length of illness was shorter for their patients. The greatest benefit of the system was that they could prescribe expensive drugs whenever indicated and thereby shorten the length of illness for their patients. Furthermore, if the patient needed hospitalization or operation, he could have it. Everyone emphasized the fact that the system permitted them to give their patients better medical care than was previously possible.

This is not a plea for the English health system, but it is a plea for the medical profession to consider the ways and means to develop the best possible program of medical care. Blue Cross and Blue Shield help with many illnesses but do not cover the catastrophic illness nor the long chronic illness of advancing years. Furthermore, many patients who can least afford to pay remain without insurance. These problems must be met. It is the duty of the medical profession to develop the medical program which will give everyone in our country the best possible medical care.

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Letters to the Editor

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To the Editor:

Dr. Robert H. Bayley recently published an article in the *American Heart Journal* ("The Application of Boundary Potentials to Several Electrocardiographic Problems" 61:684, 1961) in which he quotes from a private communication from me. These quotations are incomplete and out of context and tend to give a false impression of my statements and views. The communication in question was in the form of a commentary on Dr. Bayley's paper "Unipolar Potential Measurements in the Electric Field Produced by an Arbitrary Dipole in a Circular Homogeneous Lamina," *Circulation Research* 7:537, 1959. It is also pertinent to the present article.

Comments on Bayley's paper in Circulation Research 7:537, 1959).

BACKGROUND. Consider an arbitrary volume conductor containing electrical sources and immersed in a nonconducting fluid. There will then exist an electric potential, V, satisfying the following equations:

$$-g\Delta^2 V = J_v$$

$$g_i \Delta V|S_{ij} = g_j \Delta V|S_{ij}$$

where J_v = electrical current source distribution, g = conductivity of medium, S_{ij} = surface separating region of conductivity g_i from region of conductivity g_j. No unique solution to the foregoing equations exists. However, all solutions differ at most by a constant. Hence, if V′ and V″ are any two solutions, then

$$V' - V'' = \text{constant}.$$

Every scheme for measuring the potential must involve a series of measurements of potential difference, i.e., we must connect the voltmeter terminals to two points each time it is used. Now if the voltmeter does not affect the potentials to be measured (which can be achieved by making the voltmeter impedance much higher than the impedance between the terminals), the reading depends only on the terminal points A and B, and indeed is equal to

$$V'(A) - V'(B) = [V''(A) + \text{constant}] - [V''(B) + \text{constant}] = V''(A) - V''(B)$$

If this were not true, the concept of potential difference would be meaningless.

These statements are equally true if points A or B or both are located at the junction of a number of resistors whose other terminals are connected to a number of arbitrary points, provided that the resistor network does not affect the potential distribution.

Thus, each and every solution to the theoretical potential problem can be used to predict potential difference measurements. All solutions lead to the same value for potential difference. No solution is any better than any other. The zero of potential is perfectly arbitrary as any point can be used as a reference and assigned the value 0.

If the electrical sources in the conductor change [slowly] with time, then at each instant of time there exists a solution to the potential problem. This solution is exactly the one discussed above. At each instant of time, then, measurements of potential difference can be made. The potential at any point as a function of time is a meaningless concept unless we specify a reference potential. Furthermore, the time function must depend on the reference potential chosen, but it will not depend on which theoretical solution is used. Hence, a statement that the potential at a point changes or does not change as the sources change is utterly devoid of meaning if no reference potential is specified.

BAYLEY'S EXPERIMENT. Bayley investigated the potential on the perimeter of a circular conductor containing a dipole source. He made measurements with respect to two references: (1) the average potential appearing around the perimeter, obtained by connecting 72 equal resistors to points equally spaced 5 degrees apart on the circumference; (2) the average of the potential on the two terminals of the dipole source obtained with the use of a Wagner ground. He had previously obtained a theoretical solution for the first reference with which his experimental results checked. He did not have a theoretical solution for the second reference (which is much more difficult to obtain), but if he did, his measurements would obviously check it (by definition of solution).

What Bayley found was that for all locations of the dipole except the centric one there was a difference in potential between the two references. This fact is of no practical consequence. Either set of data would lead to the same result for the potential difference between any two points on the perimeter. Bayley's experimental set-up was poor from the mechanical standpoint. His ability to locate the dipole mechanically was not at all consistent with the ability to detect differences in locations electrically. This fact undoubtedly led to the erroneous conclusions on occurrence of voltage maxima, and to the fact that he did not obtain a smooth curve for measurements with respect to the Wagner ground in Table 4. No attempt was made to investigate the basis for the reported variation in total potential differences in the field when the two references were used. Bayley's dipole was fairly large in comparison with the dimensions of the lamina. It is entirely possible that with a dipole consisting of smaller electrodes there would have been closer agreement between the two reference

points. It is also likely that the agreement would have been better in a three-dimensional model. *In either case the results are of little more than academic interest.*

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To the Editor:

Dr. David B. Geselowitz, Ph.D. (electrical engineering), is an "old hand" at potential theory. Nevertheless, he is time-wise a "new hand" in the field of electrocardiography. Thirty-odd years ago a pioneer in basic electrocardiography, Dr. Frank N. Wilson (and associates), made the *arbitrary* choice of *zero* of *potential* at *infinity*[1] [or its *equivalent*]. It appears likely that this choice was a wise one because of its *universal mathematical convenience*, and because it preserves *symmetry* of the resultant dipole field. In the years that followed, Dr. F. N. Wilson and his co-workers introduced *Unipolar Precordial Leads* which are still in widespread use today. The very useful and elaborate interpretation placed upon these leads retains the basic concept of their *arbitrary* choice of *zero* of *potential* at *infinity*[2,3] [or its *equivalent*]. Since Dr. Geselowitz has no fundamental disagreement with this choice of reference potential (or any other reference choice), he might appear to be more accommodating and go along with electrocardiographers (physicians) or he may care to rewrite much of the last thirty years of the electrocardiographic literature. For example, would Dr. Geselowitz prefer to choose the dipole source as zero reference and demonstrate to physicians from a model that the heart's field is a host of *negative potential differences?* On the following day, would Dr. Geselowitz choose the dipole sink as zero reference and demonstrate that the heart's field is a host of *positive potential differences?* Physicians would now oscillate between a field of *negative* potential differences and a field of *positive* potential differences. Perhaps a few of the most studious physicians might seek an authoritative source on dipole potential theory for relief from their *legitimately created* quandry. If they consult the authority, Sir James Jeans (see page 27 of Reference 4), they find that he conveniently makes the wise choice identical to that adopted by Dr. F. N. Wilson. Later, on pages 50-51 of that same work, Jeans again uses, by choice, the *zero* of *potential* at *infinity* for reference in treating dipole potential theory. Dr. E. Frank and Dr. C. Kay make this same choice in their *mathematical* treatment of dipole potential theory.[5] Generally speaking, this choice for reference potential is made by all authors of texts which I have consulted on dipole potential theory.

My difference with Dr. Geselowitz centers upon his refusal to permit electrocardiographers to retain their long-established choice of reference as the *zero* of *potential* at *infinity* or its *equivalent*. Academic as this may be in the higher realms of potential theory, the physician's *arbitrary* choice *was made wisely* many years ago; and, for those who teach electrocardiography to physicians, there is a stubborn reluctance to *alter this choice now*, or, from *day* to *day*. This position *must* appear somewhat *more than academic* to those who instruct physicians in the area of electrocardiography.

Technical note. Excluding the electrode positions in the left-hand column, column 3 of Table 4[6] is that to which Dr. Geselowitz's letter refers. Column 1 of this table gives the *mathematically* predicted electrode positions in centimeters fR(P), and column 2 gives the *mechanically* measured distances using V_T as reference. A comparison of columns 1 and 2 indicates a highly satisfactory *mechanical* result. The *distance fault* in column 3 is the result of using the Frank-Kay Wagner ground potential reference V_W. In Table 5, the obvious maximal-minimal potential "fault" was known to be due to a difference in generator output or *dipole moment*. This difference is totally *unimportant* to the argument presented. The argument here is that, with any dipole moment, the line integral of the potential function with respect to V_T as reference is zero, as it should be for an analytic function. Using V_W as reference, the line integral is *not zero* because the mathematical potential difference function is *not analytic*. For example, using the dipole source as zero reference yields a group of potential differences for the boundary which are all negative and can never approach a zero average for any value of the dipole moment provided this moment exists. In the recent article[7] the Wagner ground potential function is solved in terms of certain boundary potentials. Had E. Frank and C. Kay solved this function for their torso model, they could have subtracted the Wagner ground potential from their potential difference measurements, and revised their published tables[8] for correct unipolar potentials which would have agreed with their mathematical potential functions based on their arbitrary choice of zero reference at infinity or its equivalent. The revised tables in their voltage maps would then have given an *accurate ventricular center* by an accurate *zero* of *potential* on the *boundary*.

The Geselowitz letter is certainly welcome, for it presents agreement with me, for the first time, that the E. Frank and C. Kay reference potential on the Wagner ground is *not equivalent* to the *mathematical* choice of zero of potential at infinity. The reference potential V_T of my averaging network is *equivalent* to this choice.[6,7,9-11] This equivalence has now been confirmed by other investigators.[12] Therefore, it is my present hope that these two letters to the Editor will bring the potential reference problem to a final and pleasant conclusion.

Robert H. Bayley, M.D.

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85 Jane Street
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April 13, 1961

To the Editor:

The Editorial on MER-29 in the April, 1961, issue of the *American Heart Journal* is limited mainly to a review of the by now outdated conference held at Princeton in December, 1959. Unfortunately, it misrepresents the information there brought forward.

To be specific, on page 433, it is said, and I quote: "What makes it important is that accumulation of desmosterol seems to slow down synthesis of *its* precursors . . ." No such evidence was presented. Is this strictly conjecture? Studies by Avigan, Steinberg and others published in the *Journal of Biological Chemistry*, November, 1960, do not indicate this alleged slowdown. Moreover, they show that MER-29 has no appreciable effect on *total* sterol concentration in tissues.

Next quote: "The remarkable thing is that this depletion seems to occur clinically in patients with arteriosclerotic heart disease. This has not been directly demonstrated . . ." I agree that this has not been demonstrated and wonder how it can nevertheless be remarkable. Certainly it is not demonstrated by the two prints of the identical negative, presented in Fig. 2, which are erroneously claimed to have been made 6 months apart.

Next quote: "However, studies of more than 1 year's duration at the time of the Conference, and more than 2 years now, indicate that a substantial proportion of patients with angina pectoris improve . . ." Facts are: At the Conference, Dr. Hollander reported definite reduction in anginal attacks in 10 out of 24 patients. On the other hand, Dr. Henry Russek reported that administration of MER-29 in a dosage of 250 mg. daily to a total of 40 coronary patients for a period of 3 to 5 months did not disclose evidence of clinical or electrocardiographic improvement. Dr. Halpern reported that 9 patients out of his group of 18 showed subjective improvement of angina pectoris during MER-29 therapy, but he strongly questioned whether this was at all related to a cholesterol-reducing effect of the drug. Finally, Dr. Lisan, speaking about a group of 45 patients, stated that there was an apparent improvement in the symptoms but that electrocardiographic studies generally showed no significant changes. He added that at least 5 to 10 years of study would be needed to determine the over-all prognostic significance of this drug in coronary artery disease.

In view of these reports, I am puzzled about just what is implied by the statement on page 433: ". . . the impact of the evidence lies more in its mass and direction than in any single criterion . . ." Obviously, such mass of evidence was completely lacking, and there were no protests when Dr. Wilkins stated at the Conference: "We must assume that the disease in its essence marches along in people even on MER-29."

The manufacturers of MER-29 claim many implied clinical merits for their product. They sidestep issues such as what happens to β-lipoproteins; the inadequacy of the usual colorimetric methods to determine total sterols in serum and tissues; the significance of hyperdesmosterolemia.

It should be remembered that, to the uninformed, the term "cholesterol" has gradually become a symbol for atherogenesis, and that this was permissible as long as cholesterol was the endpoint of sterol fat metabolism. However, when due to triparanol an otherwise intermediary sterol becomes the *end*product instead of cholesterol, this intermediary sterol now becomes available for deposit where formerly it would have been metabolized to cholesterol. To the unsuspecting mind, the claim that this "reduces cholesterol" may be literally true, but in everyday medical symbolism, it is highly misleading. The new endproduct should be assumed to be just as atherogenic as cholesterol unless proved otherwise. Also, those who claim that no "toxicity" has been demonstrated for the new endproduct (desmosterol) should

be reminded that no "toxicity" has been demonstrated for cholesterol either, and that atherogenicity is not taken into consideration when disclaiming "toxicity."

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July 28, 1961

To the Editor:

The Editorial of April, 1961, referred principally to the Princeton Conference, because little new data from human beings were available at the time of writing and, also because the function of an editorial is to state an informed, presumably critical opinion; it is not to be a repetitive checklist or review. The editorial did *not* misrepresent my understanding of available information.

The question of synthesis: Investigators have looked for accumulation of sterol precursors in animals and man treated with triparanol; none has been found, so that it is more than conjectural to assume that the process is slowed all along the line. As made, my statement was affirmatively based on isotopic studies in man[1] showing decreases in total body sterol content (cholesterol plus desmosterol), since reaffirmed,[2] and on decreases up to 50 per cent in peak *total* serum sterol radioactivity after injection of 2-C^{14}-mevalonate[3]; a subsequent estimate[4] is that "synthesis and delivery of radioactive sterol to the serum was 22 per cent less during treatment"; in this group, 1 patient of 9 showed on two occasions a rise in total serum sterol, and 1 showed no change, while the group averaged a 15 per cent decrease. Others have found increases in total serum sterol in 1 of 2 patients,[5] decreases averaging 10 per cent in 7,[6] and decreases averaging 19 per cent in all of 10 patients[7]; the last cited[7] emphasize that desmosterol serum levels do not *rise progressively* during treatment and infer, as I had implied, that the chemical negative feedback regulating cholesterol biosynthesis is slowed. Hence, my inference or conjecture has some support in dynamic studies. Tissue analyses in animals do not bear on this question. The real question is whether the effects observed in *most* people are enough to create a gradient from tissue to serum which will result in catabolism of *both* sterols as bile acids. This is a matter of opinion and experiment.[8] Some[4] believe that the response compares unfavorably with other means, such as diet or nicotinic acid. Others[2] advocate combined treatment in some patients and suggest a "synergistic" or at least additive action.

The statement ". . . . this depletion seems to occur clinically. . . (but) . . .has not been directly demonstrated . . ." is overcondensed and perhaps indiscreet in context and silly out of it. Actually, tissue analyses in a treated patient[2] showed virtually no desmosterol in coronary artery sterol and hepatic total sterol (83 per cent cholesterol) of only 2.28 mg. per gram. The xanthelasma shown were flatter at 6 months but this did not show in a head-on, two-dimensional print reduced for publication. The suggestion of "error"is gratuitous.

Anginal relief is a vexed and difficult field. Khellin comes to mind in this connection. Dr. Robert McMaster, of W. R. Merrell Company, informs me that, as of July 26, 1961, publications list 134 patients with angina with relief in 60 and ECG reversal in 10, and that his correspondence lists another 274 anginal patients with 67 per cent relief. Unpublished observations[9] indicate in 58 patients with ischemic heart disease subjective relief in 5, objective improvement (exercise tolerance ECG) in 3, and both in 1. The evidential value of the larger groups may be questioned: at least, the data have "mass and direction." Russek's are perhaps the most convincing to the contrary; however, his 14 subjects were selected from a large array because they gave reproducible responses to exercise—which most people do not—and it is conceivable that their anginal mechanisms may be unusual in some way.

Lipoprotein data are scant. Paper electrophoresis[10] indicates decreases in beta-lipoproteins and beta/alpha lipoprotein ratios in most patients; a review of data with Dr. Martins shows an association of anginal relief with decrease in beta/alpha ratio; this is under further controlled study. The manufacturers have not stressed inadequacy of usual methods of determining cholesterol in the presence of desmosterol, largely, I should think, because they had no information on the effect of hyperdesmosterolemia. In rabbits, desmosterol is as irritating, presumably as atherogenic, as cholesterol. Loss of hair and skin changes[12] found in some patients (to a severe degree in 2 of our group) may be related to desmosterol, but no one knows.

In summary, new data indicate unsuspected side effects in some people, but this is true of most drugs as they come into wide use, and does not alter the facts that this drug was first presented in an unusually "ethical" way, that it is an expedient that diminishes serum cholesterol and total serum sterol in most people, that it may or may not bear on the problem of cornary atherogenesis, and that the Editorial did not misrepresent either my understanding of the facts available or, fortunately, those since accumulated.

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Book reviews

CARDIOLOGY. AN ENCYCLOPEDIA OF THE CARDIOVASCULAR SYSTEM. VOLUME 5: RELATED SPECIALTY FIELDS. Edited by Aldo A. Luisada, M.D., with a foreword by Ashton Graybiel, M.D. Sponsored by the American College of Cardiology. New York, 1961, McGraw-Hill Book Company, Inc. Price $27.50.

This is the fifth and last volume of the encyclopedia conceived by Graybiel, when he was president of the American College of Cardiology, and carried through by Luisada and a number of other authors. It is a miscellany volume, designed to pick up loose ends. There is an element of surprise and anticipation as one leafs through it; much of the material is fascinating and most of it quite useful. The "reader who must run" will find it most helpful to have such a body of information collected in one spot as long as it remains reasonably current.

Part 21 (Pharmacology and the Cardiovascular System) is undoubtedly the most useful, but not perhaps the most interesting, section. It is, for the most part, authoritatively written, but some of its portions, like many symposium type of articles, tend to be unnecessarily verbose. The various authors seem to make a conscious effort to provide basic therapeutic information and to avoid controversy. Even though Part 21 is hardly the place to look up such mundane items as dosages (although they are included), it constitutes a very effective monograph, and some portions are outstanding. Vogl and Talso, for example, have handled their review of diuretic agents very well; the section on digitalis (45 pages) is well organized and informative but not very readable. The section on cardiac depressants covers the ground well but seems, to this reviewer, to leave the implication that procaine amide is less noxious than quinidine. "Quinidine is potentially a dangerous drug when employed indiscriminately . . .," the authors quite correctly point out. But, in dealing with procaine amide (in the comparable subsection), they note that "Few side effects are generally associated with the oral administration of procaine amide in the usual therapeutic doses." Actually, both drugs are dangerous if used indiscriminately and neither should be used without proper precautions. Burn's section on nicotine is interesting, as is the section dealing with anesthetic agents (Part 22).

Part 24 (medicolegal, industrial, and insurance aspects) and Part 25 (stress effects) are both impressive, with a few reservations. Of especial interest is Rotta's very succinct account of altitude effects, and Fabricant's rather curious bit titled "World Politics and Cardiovascular Disease." Jokl's section on sports and athletics contains a large amount of information but is considerably out of date with regard to exercise physiology per se.

Part 26 will delight those old enough to have begun to wonder where cardiology came from and where it is going; others can pass on to Part 27, dealing with animal cardiology. Both parts are imaginatively done. Fishbein's short summary on cardiological bibliography is necessarily very incomplete but again points up the need for a thorough, properly annotated bibliography in the cardiovascular area. The animal section will interest those doing animal experimentation and contains information not readily available elsewhere.

In short, this is an unexpectedly interesting conglomerate of cardiological information and should be useful to practitioner and investigator alike.

Renale Hämodynamik, Wasser-und Elektrolytausscheidung bei Hypertonie. By Paul Cottier, Basle and Stuttgart, 1960, Benno Schwabe & Co., 180 pages. Price: Sw. Fr. 15. Sole U. S. and Canadian representative is Intercontinental Medical Book Corp., New York, N. Y. Price $4.

This book represents an impressive amount of work centered around the phenomenon of increased natruresis observed under certain conditions in hypertensive patients. The author considers that this phenomenon is a result of the elevated renal blood pressure and is independent of the factors which might play a role in the etiology of essential hypertension.

The road to this conclusion was an arduous one. The author studied alterations in renal function and hemodynamics in hypertensive states; diuresis and natruresis under resting conditions and after oral and parenteral fluid and sodium chloride loading; the effect of sodium chloride loading upon renal hemodynamics; the effect of changes in the extracellular fluid volume (ECV) and exchangeable sodium upon natruresis and chloruresis in hypertension; and the correlation between the rate of aldosterone secretion (measured by the urinary excretion of aldosterone) and natruresis. He also attempted to correlate the grade of hypertension with the degree of pathologic changes in the target organs.

Many studies of this type have been reported previously. However, in an area as confused by contradictory reports as this one, repetition is necessary. What disturbs the reviewer is that by focusing, perhaps too sharply, on one aspect of the problem, the author appears to lose his perspective at times. In some of his studies he uses a mathematical "medium arterial pressure," $\frac{\text{systolic - diastolic,}}{2}$ erroneously referred to as "mean arterial pressure" in the English summary, as a measure for grading the severity of hypertension. Unfortunately, this formula, which has also been used by others, would place a patient with a blood pressure of 180/120 mm. Hg in the same category as one with 210/90 mm. Hg. One wonders whether this makes much difference to the author. Indeed, in some chapters he creates the impression that he doubts the basic difference

between essential hypertension and an elevation of systolic blood pressure in arteriosclerosis. His caution in expressing himself on this and on some other subjects amounts to ambiguity. At the same time, he is quite unequivocal in stating that the variations in the ECV, in the exchangeable sodium, and in the aldosterone secretion have been ruled out as possible factors in the hypernatruresis. This is an overstatement. The well-documented findings of Gamble, of Strauss and co-workers, Bartter and co-workers, Crawford and Ludemann, and, more recently, of Baldwin and associates, do not appear to have been disproved by the author's studies. Nor does the author's purely speculative theory of "fluctuating renal vasospasm" replace the concept of H. W. Smith in explaining the time-lag phenomenon of sodium excretion.

This work clarified some hitherto blurred details in this field, and that is a contribution. The book does not produce new facts of basic importance, but the sheer mass of data accumulated in it and the extensive discussion of the findings of others make this volume useful for students of hypertension and electrolyte metabolism. The chapter in which a report is made on a comparative study of the effect of prolonged hypotensive therapy with a single drug (reserpine, hydralazine, chlorothiazide, mecamylamine) will be of interest to clinicians.

EINFÜHRUNG IN DIE PHYSIOLOGIE DES MENSCHEN (Introduction to the Physiology of Man). By Hermann Rein; 13th and 14th revised editions issued by Max Schneider, Professor der Physiologie, Direktor des Instituts für Normale and Pathologische Physiologie der Universität Koln. Berlin, 1960, Springer-Verlag, 493 illustrations, 765 pages. Price: DM 59.60.

The textbook of physiology by Hermann Rein had had 10 editions before the death of the author. After that it was issued by his pupil Max Schneider. Comparing the recent thirteenth and fourteenth editions with the former ones, the reader is readily aware of the great increase in knowledge in the field of physiology that has been attained during the past 10 years. In spite of the voluminous increase of facts, Schneider has been successful in maintaining the basic concepts of his teacher. The special aim of the book is to present scientific interpretations for the physiologic facts of life and to provide understanding for their interrelationships. For this purpose a great number of single facts are described on a broad scale to reveal the physiologist's method of combination and correlation of physiologic events. The part concerning the heart and peripheral circulation is described in detail because of its great importance to the practitioner. Here the cardiologist will find all the interesting physiologic reactions of stimulation of the heart, innervation of the heart, cardiac dynamics, changes of shape of the heart during contraction, of the heart-valve-systems, and of energy metabolism—all these facts are presented according to the latest knowledge. The cardiologist will also be interested in the description of the peripheral circulation, in renal physiology, and in fluid and electrolyte metabolism; these too are presented in the most modern aspects. All in all this is a textbook which reveals the newest platform of scientific knowledge in physiology, and it is presented in an excellent and comprehensive manner.

CARDIAC PROBLEMS. Edited by K. Shirley Smith, B.S.C., M.D., F.R.C.P., Physician and Cardiologist to the Charing Cross and London Chest Hospitals, with the aid of sixteen contributors. Papers read at three symposia: Part I, Symposium held Dec. 6, 1957; Part II, Symposium held July 15, 1959; Part III, Symposium held June 8, 1960. The Chest and Heart Association, Tavistock House North, Tavistock Square, London, England. London, 1961, Waterlow & Sons, Ltd., 144 pages. Price $3.50.

The papers presented in this small volume were originally given by a group of British cardiologists at three symposia, held in 1957, 1959, and 1960. Revised and brought up to date, these papers cover a wide range of subjects in heart disease, including cardiopulmonary disease, heart failure, hypertension, the surgical treatment of heart disease, and the management of coronary disease. The emphasis is primarily on clinical aspects of disease, although physiologic mechanisms are frequently invoked to further understanding.

In general, the papers strike a note of excellence and brevity, and they will be of interest to most students of heart disease. Although the emphasis on the utilization of physiologic mechanisms primarily for the recognition and management of clinical problems may be somewhat heretical in the eyes of some American readers, the directness and simplicity of these papers is refreshing. Of particular interest is the chapter on endocrine aspects of heart failure; although possibly overly simplified, it is stimulating and provocative.

Announcements

AN INTERNATIONAL RESEARCH CONFERENCE ON FAT AS A TISSUE will be held on Thursday and Friday, Nov. 1 and 2, 1962, at the Lankenau Hospital, Philadelphia 51, Pa.

A MEDICAL CONTINUATION COURSE, Intermediate Electrocardiography for General Physicians and Specialists, is to be presented at the Center for Continuation Study, University of Minnesota, Minneapolis, Minn., on Jan. 2-6, 1962.

For further information concerning this course, write to the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14, Minn.

SPECIAL PROGRAM FOR RESEARCH GRANTS IN RADIOLOGICAL HEALTH: In view of the rapid expansion which is forecast in the use of nuclear energy, x-rays, and other sources of radiation, a greatly expanded program for research grants in the field of radiological health has been developed. These grants are offered to support research by individuals, universities, hospitals, laboratories, and other public or private institutions in the assessment and control of man-made and natural radiation exposures to the individual, no matter how the separate components may originate. The knowledge and skills of many professional disciplines and specialties—physicians, engineers, physicists, chemists, educators, statisticians among them—are needed to find answers to the many challenging questions in radiological health.

Research proposals should contribute to the determination of the extent and character of the radiation problem as well as the mechanisms by which radiation produces damage. Studies aimed at the elucidation of the radiation damage "cause and effect" relationship are essential if low-level and long-term radiation exposure effects are to be accurately assessed and general control programs organized. Therefore, basic studies relating to critical body organs and systems, preferred metabolic pathways for specific radioactive contaminants, and an understanding of the radiosensitizing and modifying effects of various materials are encouraged.

Broad epidemiological studies aimed at a scientific evaluation of the long-term effects, such as aging, congenital malformations, genetic effects, behavioral patterns, and induction of cancer, are also of primary concern. Field studies of the movement of radioactive contaminants in biota and human food chains are of special interest, since we know that the physical environment may be greatly altered by biological activity, as for example, the concentration of water-borne radionuclides in microorganisms and fish.

Purely physical studies, such as chemical mechanisms in radiation chemistry, the design of equipment, and the development of techniques to accurately assess or reduce the population dosages, are mandatory for a successful research program.

Studies aimed at directing scientific findings toward control devices or procedures are necessary in a "total view" of man's ecological system, as are studies that attempt to assess the relationship between health hazards created and possible benefits derived by radiation usage. The determination of the consequences of radiation exposure for present and future generations will require intensive investigation.

For information and/or application forms, write to Dr. Paul F. Hahn, Chief, Office of Extramural Grants, Division of Radiological Health, U. S. Public Health Service, U. S. Department of Health, Education and Welfare, Washington 25, D. C

REPORT ON POSTGRADUATE PHYSICIAN EDUCATION: A report on the status and aims of postgraduate medical education, planned to serve as a guide to future activities in this field, has just been published by the American Heart Association. Entitled "The Physician's Continuing Education," the report was prepared on behalf of the Association's Committee on Professional Education by a group of 13 volunteer physicians headed by Dr. Stewart G. Wolf, Oklahoma City, Okla.

According to the report, an analysis of current activity in the field of postgraduate medical education indicates that present techniques reach relatively few physicians. It notes that training programs have not always been adapted to the needs of practicing physicians.

The report discusses various educational techniques for postgraduate or "continuing" education in terms of their relative merits, and emphasizes the need for research to develop new training methods as well as to improve evaluation of those now currently used. It concludes with recommendations for a new and vigorous approach to the problem by the Association and its affiliates, outlining a number of pilot projects which will involve participation by affiliated Heart Associations on a selective basis. The ultimate goal of the pilot studies is to improve medical care for patients with cardiovascular disease.

Copies of the report, a 48-page paper-bound volume, may be obtained from local or state Heart Associations or through the American Heart Association, 44 East 23rd Street, New York 10, N. Y., at 60 cents per copy.